Endocrine Abstracts

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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/eje.aspx. This year’s recipient is Dr Robert Semple. The prize will be presented as part of the ECE 2015 opening ceremony where Dr Semple will deliver his lecture. Dr Semple will also write a review article based on this lecture to be published in the European Journal of Endocrinology.

Robert Semple, University of Cambridge, UK

Robert Semple is a Wellcome Trust Senior Research Fellow and Honorary Consultant Endocrinologist at the University of Cambridge, UK. He read Biochemistry and then Medicine at the University of Cambridge before internal medical posts in London. He returned to Cambridge for specialist training in Diabetes and Endocrinology, interrupted by doctoral studies with Prof Sir Stephen O’Rahilly, focussing on transcriptional regulation of adipose tissue metabolism.

For the past 12 years he has focussed on rare disorders of insulin action and growth. His research aims to identify novel genetic defects underlying insulin resistance and related conditions, both to accelerate diagnosis and to enhance treatment of affected patients, and to draw inferences, through physiological study of affected patients, about the pathobiology of common forms of metabolic disease. This work has played a key part in the establishment of a National Severe Insulin Resistance Service in Cambridge.

Dr Semple is also a fellow of Clare College, Cambridge, and Director of the Cambridge MB PhD programme.
Insulin Action in Common Disease: Too Much, Too Little, or Both?

Robert Semple, Wellcome Trust Senior Research Fellow and Honorary Consultant Endocrinologist, The University of Cambridge, Cambridge, UK

Insulin resistance is usually taken to mean a state in which insulin exerts a diminished blood glucose lowering effect. Insulin resistance is not a disease in itself, but is closely associated with pandemic diseases or tissue pathologies including type 2 diabetes, fatty liver, metabolic dyslipidemia, polycystic ovary syndrome and some cancers. It is also closely associated in the general population with obesity, and there is a widely prevalent view that obesity leads to insulin resistance, and that it is when compensatory hyperinsulinaemia starts to fail that diseases ensue. Nevertheless the idea has been promulgated since the 1980s that major components of the ‘insulin resistance syndrome’ are actually consequences of high levels of insulin exerting harmful effects on responsive tissues. In this talk known single gene forms of insulin resistance will be compared and contrasted with prevalent insulin resistance and with insulin deficiency in order to assess the relative importance in humans of lack of insulin action and, conversely, excessive insulin action in disease pathogenesis, with particular reference to fatty liver, dyslipidaemia, polycystic ovary syndrome and soft tissue overgrowth.
Geoffrey Harris Prize Winner UK

This prestigious prize is intended for established workers in the field of basic and clinical neuroendocrinology and is generously supported by Ipsen. This year’s recipient is Prof. Carlos Dieguez. The prize will be presented as part of the ECE 2015 opening ceremony where Prof. Dieguez will deliver his lecture. Prof. Dieguez will also deliver two other lectures at future ESE scientific meetings. Further information can be found at http://www.ese-hormones.org/prizes/

Prof. Carlos Dieguez, Professor of Physiology, Scientific Director, Center for Medical Research, University of Santiago de Compostela, Spain

Prof. Carlos Dieguez graduated in Medicine at the University of Santiago de Compostela in 1979. From 1981 to 1987 he completed his PhD and postdoctoral training under the supervision of M. Scanlon at the Department of Medicine, the Welsh National School of Medicine in Cardiff (UK). During this period the main focus of his research was related to the neuroendocrine control of TSH and GH secretion.

In 1988, he returned to the University of Santiago de Compostela where he is currently Professor of Physiology and Scientific Director of the Center for Medical Research. He has published over 450 research papers and reviews. His work has been focused in the neuroendocrine control of pituitary hormone secretion, energy balance and peripheral lipid metabolism.

His group maintains a large number of collaborations with different endocrine groups in Europe as well as being part of different consortiums funded by the EU (Diabesity, Neurofast, Reprobesity, Trans-in).
The Geoffrey Harris Prize Lecture

Understanding energy sensors, understanding neuroendocrine function

Carlos Dieguez, University Santiago de Compostela, Santiago de Compostela, Spain

The question on how cells, tissues and organisms are able to detect energy/nutrient availability has been the focus of research for many years. Data gleaned recently have identified different nutrient-sensing circuits implicated in the regulation of different homeostatic process. Furthermore, there has been a steady increase in our knowledge regarding the cellular and molecular mechanisms involved in nutrient detection and integration. In particular, this has allowed for a better understanding of the neural and endocrine circuits involved in nutrient and energy sensing and their adaptation to different metabolic needs in a tissue-specific manner.

Work carry out by different groups have uncovered the mechanism by which hypothalamic neurons sense nutrient bioavailability, with a relevant contribution of AMPK and mTOR among others, as sensors of cellular energy status. Interestingly, the orexigenic/anorexigenci effects of different neuropeptides and peripheral hormones appear to be mediated by an AMPK-driven regulation of hypothalamic lipid metabolism, and may involve also the modulation of mTOR signaling. Their integrative role in terms of energy homeostasis involved different mechanisms including regulation of food intake, energy expenditure or metabolic homeostasis at relevant target tissues. Furthermore recent developments has shown the involvement of central energy sensors in orchestrating the adaptative response of different hypothalamic-pituitary axis to changes in energy availability. This development helps to understand the interplay between peripheral signals and central neurotransmitters and neuropeptides in order to elicit a biological response at the whole organism.
Plenary Lectures
The most common form of congenital adrenal hyperplasia is 21-hydroxylase deficiency (21OHD). The treatment for classic (severe) 21OHD differs from treatment of most other types of adrenal insufficiency in that not only must one replace the glucocorticoid and mineralocorticoid deficiency but also attenuate the high adrenal-derived androgen production. In order to reduce the adrenal corticotropin (ACTH) driven androgen production, supraphysiologic doses of glucocorticoid and/or long-acting synthetic glucocorticoids are often used, to compensate for the short half-life of oral hydrocortisone. In particular, the early morning rise in ACTH and adrenal steroids is difficult to manage in 21OHD. Consequently, adults with 21OHD suffer from high rates of obesity, low bone density, and cushingoid features. Several strategies have been employed recently to improve the control of androgen excess in 21OHD while limiting the dose of glucocorticoid to the physiologic replacement range. Modified-release forms of hydrocortisone have been developed to prolong its half-life, and hydrocortisone has been delivered via a continuous subcutaneous infusion system, to match the dosage and timing to the clinical need. Abiraterone acetate, the prodrug for the potent 17-hydroxylase/17,20-lyase (CYP17A1) inhibitor abiraterone, markedly lowered androgens in six adult women with 21OHD in a short-term study of 100–250 mg/day. The non-steroidal antagonist of the corticotropin-releasing factor receptor type 1 (CRFR1), NBI-77860, lowered ACTH and 17OHP in eight adult women with 21OHD. These therapies are all under further study to determine safety and efficacy in children and adults.

In addition, the pathways of androgen excess in 21OHD have been unclear, and the best biomarkers for diagnosis and titration of therapy are debated. Recent work suggests that the alternate or ‘backdoor’ pathway to dihydrotestosterone via 5α-reduced precursors significantly contributes to the androgen excess of infants with 21OHD. Specific 21- and 19-carbon steroids of adrenal origin might be better biomarkers of 21OHD than 17-hydroxyprogesterone and testosterone.

Disclosure
Janssen Research and Development and Neurocrine Biosciences provided funds for contracted research.

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Initiative for Science in Europe (ISE) - how can we lobby so that Europe listens?

PL6

Abstract unavailable.

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Obesity and the skeleton

PL7

Obesity and the skeleton
Juliet Compston
Cambridge Biomedical Campus, Cambridge, UK.

Until recently obesity was believed to be protective against fractures as a result of higher bone mass and the protective effect of subcutaneous fat during falls. However, recent studies indicate that fractures in obese postmenopausal women and older men make a substantial contribution to the overall fracture burden in these populations. The effect of obesity on fracture risk is site-dependent, with protection against hip and wrist fractures but increased risk of ankle and lower leg fractures.

The pathophysiology of bone fragility in obese individuals has not been clearly established. Adipose tissue can produce adipokines and cytokines, many of which have adverse effects on bone. Increased intramuscular adipose tissue is likely to contribute to reduced muscle strength, reducing bone mass and increasing the risk of falls. Other potential pathogenetic factors include vitamin D insufficiency, secondary hyperparathyroidism and hypogonadism.

The evidence for efficacy of anti-osteoporosis medication in the obese is weak, since pivotal clinical trials have included relatively few obese individuals. There is some evidence that anti-resorptive medications may not be effective in reducing non-vertebral fractures in obese postmenopausal women. Further studies are needed to enable the development of effective strategies to reduce the growing fracture burden in the obese population.

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From base change to better care in diabetes

PL8

Abstract unavailable.

DOI: 10.1530/endoabs.37.PL8
Symposia
**Glucocorticoid action in health and disease**

**S1.1**

**Dietary regulation of cortisol production and metabolism in humans**

Brian R Walker

University of Edinburgh, Scotland, UK.

The hypothalamic-pituitary adrenal (HPA) axis plays a key role in the metabolic response to stress, so it is to be anticipated that cortisol signalling might in turn be regulated by nutritional status. This regulation might operate either centrally, controlling ACTH and hence plasma cortisol, or peripherally, controlling metabolism of cortisol in target tissues. Plasma cortisol levels are elevated during starvation in animals and a recent meta-analysis confirms that starvation elevates plasma cortisol also in humans, although the effect may be transient. Cortisol levels also rise transiently after meals in humans. It is usually assumed that these effects of starvation and feeding are mediated by central alterations in the HPA axis. However, using stable isotope steroid tracers and test meals with different macronutrient components, we demonstrated that enhanced peripheral regeneration of cortisol contributes substantially to the rise in plasma cortisol after consumption of carbohydrate but not fat. We further demonstrated acute up-regulation of 11β-HSD1 activity in vivo by insulin but not lipid infusions.

With chronic dietary manipulation in humans, however, a low carbohydrate diet induces up-regulation of 11β-HSD1, an effect which is mimicked by metformin administration, suggesting that hyperinsulinaemia may chronically down-regulate 11β-HSD1. Indeed, in obesity without diabetes 11β-HSD1 is down-regulated in liver. However, other factors may come into play in obesity, particularly up-regulation of adipose 11β-HSD1 induced by intra-adipose inflammation. A complex regulation of 11β-HSD1 by pathways involved in nutrient signalling appears to be species- and tissue-specific, e.g. Tfh changes induced by PPAR agonists and growth hormone in mice not readily recapitulated in humans.

We conclude that both the HPA axis and peripheral regeneration of cortisol are influenced by nutritional status and dietary macronutrient content. Variations in glucocorticoid signalling may therefore contribute to adverse effects not only of total calorie excess, but also specific dietary components.

**Disclosure**

British Heart Foundation.

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**S1.2**

**Subclinical Cushing’s syndrome and cardiovascular disease**

Guido Di Dalmazi

Medizinische Klinik und Poliklinik IV - Klinikum der Universität München, Munich, Germany.

Subclinical Cushing’s syndrome, defined as evidence of alterations of the HPA axis in patients without stigmata of hypercortisolism, is a frequent finding among patients with adrenal incidentalomas. It is well-known that this condition is associated with several co-morbidities, such as hypertension in 2/3 of the cases, diabetes in 1/3, and dyslipidemia, which impair the cardiovascular risk profile of those patients. Recently, different independent reports on the natural history of subclinical hypercortisolism have highlighted an association of this disease with severe cardiovascular outcomes. Specifically, during a long-term follow-up surveillance period, patients with subclinical hypercortisolism show an increased incidence of cardiovascular events, mainly coronary heart disease and stroke, with respect to patients with non-functioning adrenal incidentalomas. Interestingly, an even higher risk of cardiovascular diseases was reported in patients with increased cortisol secretion during follow-up. Moreover, patients with subclinical hypercortisolism also have a reduced survival rate than those with non-functioning tumors, mainly due to cardiovascular events and infectious complications. Increased cortisol levels were independently associated to the increased cardiovascular events and mortality of those patients. It is clear that the hypercortisolism driven by these tumors, although of mild entity, plays a pivotal role in contributing to the worsened cardiovascular profile, when sustained and prolonged for several years. However, although all these data together do not provide enough evidence that the surgical treatment is the best therapeutic option for all patients with subclinical hypercortisolism, they give clues on the existence of different subtypes of diseases that must be better stratified according to the cardiovascular risk and assigned to different follow-up strategies. In this context, randomized trials focused on the efficacy of surgery on cardiovascular outcomes, on one side, and pre-operative steroid profiling with mass spectrometry, on the other side, will be extremely useful in pursuing a sub-classification of patients with subclinical hypercortisolism that could benefit from either medical or surgical treatment.

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**S1.3**

**11β-hydroxysteroid dehydrogenase type 1: substrate promiscuity, implications for local glucocorticoid activation?**

Alex Odermatt

University of Basel, Basel, Switzerland.

11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) essentially catalyzes the conversion of the inactive endogenous glucocorticoid cortisol (11-dehydrocorticosterone in rodents) and the synthetic prednisone into the active cortisol (cortisosterone in rodents) and prednisolone. The association of an elevated expression of 11β-HSD1 with metabolic disease has been extensively studied in humans and in rodent models. It is generally assumed that the effects that are observed upon modulating 11β-HSD1 function by pharmacological inhibition or genetic manipulation in transgene mouse models are glucocorticoid-dependent. However, 11β-HSD1 is a multi-functional carbonyl reductase involved in the hepatic metabolism of various non-steroidal xenobiotics. Besides, it has a role in the metabolism of neurosteroids, oxidized cholesterol and bile acids. In as much these alternative substrates might affect 11β-HSD1-dependent glucocorticoid activation can, so far, only be estimated from in vitro studies, and further investigations in vivo are needed.

A recent study in 11β-HSD1 deficient mice revealed elevated concentrations of circulating free bile acids, an effect that was more pronounced in global than liver-specific knockout mice. A reduced expression of the bile acid coenzyme A ligase Fatp5 suggested an impaired bile acid amimation and subsequently decreased conjugation. These effects of the lack of 11β-HSD1 activity seem to be glucocorticoid-independent because intra-hepatic corticosterone levels and glucocorticoid receptor target gene expression were not decreased in livers from liver-specific knockout mice. Furthermore, Fatp5 expression was not altered in mice deficient in hepatic glucocorticoid receptors.

Thus, the elucidation of glucocorticoid-independent functions of 11β-HSD1, such as its role in oxysterol and bile acid homeostasis, and the relevance for metabolic and immune disorders warrants further investigations.

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**S2.1**

**Management of type 2 diabetes: State of the art**

Peter Rossing1,2,3

1Steno Diabetes Center, Gentofte, Denmark; 2NNF Center for Basic Metabolic Research, University of Copenhagen, Copenhagen, Denmark; 3Health Aarhus University, Aarhus, Denmark.

Hypertension is a major risk factor in type 2 diabetes both for cardiovascular and microvascular complications. It has been estimated that hypertension contributes to 41% of the attributable risk for mortality. Proper assessment of blood pressure, consideration of diurnal pattern, white coat and masked hypertension is important. Lifestyle factors should be addressed in the management, but in most patients pharmacological intervention is needed. The optimal intervention usually requires a combination of agents, particularly in patients with hypertension and renal complications, where three antihypertensive agents on average are used. Therefore selection of the optimal combination with best effect and least side effects are important, which requires attention to individual factors such as renal complications, history of cardiovascular events, fluid balance and electrolyte status. In addition attention to occurrence of side effects, as well as adherence to treatment regimen is important factors. Here consideration of the multifactorial intervention applied in type 2 diabetes is important. It is always a matter of discussion when to start treatment, as well as target blood pressure for treated individuals. Although targets have been declining for decades, to 130/80 mmHg, many of the most recent guidelines suggest a higher target blood pressure, such as 140/90, and probably as for glucose management, a need for a more individualised approach both regarding onset of treatment and target. This debate is fuelled by lack of clear evidence for the optimal target. Finally antihypertensive agents may play an important role in preventing the microvascular complications even in ‘normotensive’ subjects.

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**Endocrine Abstracts (2015) Vol 37**
S2.2
Blood glucose management
Kåre Birkeland
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Glucose lowering treatment in patients with type 2 diabetes aims at reducing hyperglycaemic symptoms, preventing acute hyperglycaemic crisis and delaying the onset and progression of macrovascular and microvascular complications. The impact of glucose control on cardiovascular complications remains uncertain, however, a modest benefit is likely to be present. The cornerstones of treatment remain education, motivation and counseling on healthy eating behavior and moderate physical activity. As only a minor proportion of subjects will reach glycaemic targets with these measures alone, pharmacological antihyperglycaemic treatment is indicated in most patients. Despite non-convincing hard evidence, metformin is the first drug of choice for those who can tolerate it, starting with low dose and increasing slowly. When insufficient to control hyperglycaemia, sulphonylureas have been the drug of choice to combine with metformin for many decades. However, its use has been challenged by epidemiological and experimental studies of possible serious side effects, although recent reviews fail to show evidence of harm of second and third generation agents. DPP4-inhibitors that increase endogenous incretin responses have a favorable side effect profile, particularly less hypoglycaemia and weight-gain than SU, however to a considerable higher cost. Although some safety data from medium-time follow-up studies begin to emerge, we will have a lot more data from hard-endpoint studies in the next 1–2 years. SGLT2-inhibitors that increase urinary glucose (an energy) loss, also compare favorably to SU regarding hypoglycaemic risk and effects on body weight. However, we still await the results of the first end-point studies with these agents, and their use should be limited to patients that cannot tolerate other agents or have special needs. Despite several new classes of oral antihyperglycaemic agents, injection therapies with insulin and/or the new GLP1-agonists is needed after many years of type 2 diabetes in a significant proportion of individuals. A single daily dose of basal insulin in a treat-to-target regimen in combination with metformin is usually the preferred start of injection therapy. It is easy to handle, relatively cheap and will often allow reaching glycaemic aims. However, it requires at least some blood glucose monitoring by the patient, it may result in weight gain and increase the risk of hypoglycaemia. The use of GLP1-agonists usually requires less BG monitoring, will reduce body weight 2–4 kg, and seldom give hypoglycaemia. However they are more expensive than insulin in most cases and there are lack of long-term outcome studies. The large and increasing number of antihyperglycaemic agents enable us to individualize treatment regimens, to maximize effects and minimize side effects and costs.

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S2.3
PCSK9 antibodies for the treatment of hypercholesterolemia
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Cardiovascular disease (CVD) is the leading cause of death worldwide accounting for more than 17 million deaths just in 2012. A major culprit for the development of CVD is an elevated low density lipoprotein (LDL) cholesterol (LDL-C) concentration. Despite statin therapy a high residual risk of cardiovascular events remains, especially since with the currently available treatment options only ~50% of high risk patients and ~20% of very high risk patients achieve their target LDL-C values of < 100 and < 70 mg/dl respectively. It is therefore clear that additional therapies are needed. The serine protease proprotein convertase subtilisin/kexin type 9 (PCSK9) binds to LDL receptor (LDL-R) and directs it to lysosomes for intracellular degradation. This results in, decreased numbers of LDL-R available on the hepatic cell surface to bind LDL particles and remove them from the circulation and therefore to a subsequent increase in circulating LDL-C concentrations. Since 2003, when the role of PCSK9 in LDL-C metabolism was discovered, there have been major efforts to develop efficient and safe methods to inhibit it. Amongst those, monoclonal antibodies against PCSK9 are the furthest in development, with multiple phase 3 trials already published and with cardiovascular endpoint trials currently underway. Two fully human monoclonal antibodies, evolocumab and alirocumab, have been extensively studied in a wide range of subjects, such as those with statin intolerance, as an add-on to statin therapy, as a monotherapy and in patients with familial hypercholesterolemia. PCSK9 antibodies result in a consistent and robust decrease in LDL-C plasma levels ranging from 40% to 70%, either on top of statins or as monotherapy. If the safety data from the on-going phase 3 trials remain as reassuring as the data available till now, PCSK9 antibodies will offer a novel, powerful therapeutic option to decrease LDL-C plasma levels and, hopefully, cardiovascular risk.

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Non-classical causes of hypopituitarism (Endorsed by Endocrine Connections)

S3.1
TBI: whom to screen for hypopituitarism
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Traumatic Brain Injury (TBI) is a devastating neurological emergency, usually resulting in transient or permanent neurological dysfunction. It is the most common cause of death and disability in young adults in industrialised countries and is a major public health problem. Although anatomical pituitary damage following TBI was first recognised as long ago as 1918, evidence of hormonal dysfunction in both the acute and chronic phases following TBI had only been studied in detail over the last twenty years. There is now a rapidly growing evidence base showing that TBI may lead to both acute and long-term anterior and posterior pituitary dysfunction. However, it is often difficult to define what constitutes anterior pituitary damage in the acute period following TBI, as opposed to the acute adaptive hormonal changes which occur in most critically ill patients. Furthermore, given the huge numbers of patients who sustain a TBI, it is not possible to perform dynamic testing to screen for the presence of long-term hypopituitarism in all survivors of TBI. This talk aims to summarise the evidence base on the incidence of both acute and long-term anterior and posterior pituitary dysfunction following TBI, and outline a pragmatic strategy to identify those who are most likely to benefit from dynamic pituitary testing.

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S3.2
Genetic causes of hypopituitarism
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Genetic causes of anterior pituitary hormone deficiencies may result in combined or isolated pituitary hormone deficiencies. These disorders represent a heterogeneous group of rare diseases leading to defective function of specific pituitary cell types. Since the first description of POU1F1 human mutations, several other genetic defects of transcription factors have been reported with variable degrees of phenotype-genotype correlations. However to date, despite the identification of a growing number of genetic causes of isolated or multiple pituitary deficiencies, the etiology of most (80–90%) congenital cases of hypopituitarism remains unsolved. Identifying new etiologies is of importance as a post-natal diagnosis to better diagnose and treat the patients (delayed pituitary deficiencies, differential diagnosis of a pituitary mass on MRI...), and as a prenatal diagnosis to decrease the risk of early death (undiagnosed corticotroph deficiency for instance).

Some patients harbour a complex phenotype including anterior pituitary hormone deficiencies in association with extra pituitary abnormalities or malformations on MRI such as pituitary stalk interruption syndrome or midline defects. The transcription factors genes involved in these phenotypes (for instance LHX3, LHX4) are early expressed in regions that determine the formation of forebrain and related midline structures such as the hypothalamus and pituitary. Mutations in these genes are therefore characterized by marked phenotypic heterogeneity. Among more recently identified forms, the DAVID syndrome, an association of a deficit in adrenocorticotropic with recurrent infections due to variable immunodeficiency was recently associated with NFKB2 mutations. In contrast, ‘pure’ endocrine phenotypes include anterior pituitary hormone deficiencies (progressive or not) with normal hypothalamo-pituitary morphology at MRI (regardless of the size of the pituitary gland) and no extra pituitary malformation. They are due to mutations of late-acting pituitary specific transcription factors. In such a context, PROP1 gene mutations remain the most frequently reported genetic defect.

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Pituitary dysfunctions, reported as ‘hypopituitarism’ or ‘hypophysis’, are relatively common side-effects induced by monoclonal antibodies (mAbs) inhibiting specific immune checkpoints. In particular, hypophysis represents a distinctive side effect of CTLA4-blocking antibodies and is a new form of autoimmune pituitary disease.

In initial trials, the incidence of hypophysis induced by anti-CTLA4-mAbs (ipilimumab and tremelimumab) varied considerably (0–17%) and seemed to be dose-dependent. Higher rate of hypophysis (14%) is associated with the administration of ipilimumab in combination with bevacizumab, while, on the other hand, hypophysis was not reported in patients treated with ipilimumab and pretreated with chemotherapy or radiotherapy, suggesting that the immune cell depletion induced by cytotoxic chemotherapy and radiotherapy may prevent mAbs induced pituitary dysfunctions. Tremelimumab has been reported to induce hypophysis in 0–2.5% of patients.

Presenting symptoms of mAbs-induced hypophysis are not specific, including headache, fatigue, weakness, while visual impairment may occur, but less frequently compared with classic lymphocytic hypophysitis (LH). At MRI a pituitary swelling can appear sometimes with thickening of the stalk. As in patients with classic LH, high-dose glucocorticoids are used to treat anti-CTLA4 hypophysis, but pituitary hormones deficits may be prolonged or even lifelong, despite the prompt initiation of glucocorticoid therapy.

Moreover, cases of hypophysis have been attributed also to interferons (with or without ribavirin) in patients affected by hepatitis C. No cases of pituitary dysfunction were reported with lamibrolizumab, a mAb against PD1.

In conclusion, hypophysis and hypopituitarism represent possible side effects of anticancer drugs. This is a real recent knowledge, because until the advent of anti-CTLA4-mAbs, hypophysis was never described in association with anticancer drugs. The precise mechanism of injury to the endocrine system triggered by these drugs is still to be fully elucidated but these conditions must be promptly recognized because they may be life-threatening.

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Thyroid hormone and cardiovascular system

Subclinical hypothyroidism and cardiovascular consequences in childhood

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The relationship between subclinical hypothyroidism (SH) and cardiovascular (CV) risk is still matter of debate. While the key-role of thyroid hormones in modulation of several atherosclerotic factors is well established, the mechanisms of TH’s action on CV system are still largely unknown.

In adults with SH a pattern of CV abnormalities (dyslipidemia, insulin resistance, endothelial and diastolic dysfunction) has been observed even in mild SH cases, indicating an improvement in the lipid profile and left ventricular function. It is well known that risk factors accelerating the development of atherosclerotic disease begins in childhood and may be predictive of CV risk in adulthood. Whether SH in children predisposes to adverse CV outcomes in adulthood is still unclear. Data on children are scanty and most of the studies are limited by the small number and the heterogeneity of the populations studied and by the presence of several confounding factors, as obesity and autoimmune, making the evaluation of the direct impact of SH on CV risk difficult.

Recent data from a selected population of subjects with mild long-lasting idiopathic SH suggested that untreated SH children may develop a cluster of subtle metabolic abnormalities as increased abdominal adiposity and slight alterations in lipid profile and homocysteine levels. The clinical significance of these changes as early steps in initiation of atherogenesis is difficult to establish. Therefore, although further studies evaluating the long-term CV consequences of childhood-onset SH and the effect of L-T4 therapy are still to be made, the evidences available suggest that these children should be carefully monitored for metabolic complications that may expose them to an higher risk of future CV diseases.

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Cardiovascular impact of thyroid hormone receptor mutations

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The actions of thyroid hormones (TH) are mediated by receptors (TRα1, TRβ1, TRβ2), encoded by separate genes (THRA, THRβ1, THRβ2), with differing tissue distribution. TRβ2 mediates negative feedback within the hypothalamic-pituitary axis, with TRβ1 being expressed in the liver & kidney; TRα1 predominates in the myocardium and skeletal muscle.

Resistance to Thyroid Hormone, usually due to heterozygous TRβ mutations (RTHβ), is characterised by elevated TH and non-suppressed TSH levels. Cardiac features include tachycardia and atrial arrhythmias; indices of myocardial contractility are in the hypertrophy range. Marked cardiac hypertrophyism in rare, homozygous RTHβ can lead to life-threatening cardiac failure. Management of cardiac features in RTHβ includes beta blockade, antiarrhythmics or lowering TH levels with triiodothyroacetic acid (TRIAC). It is not known whether raised cholesterol and triglyceride levels, hepatic steatosis and insulin resistance in RTHβ confers excess cardiometabolic risk, but TRβ-selective thyromimetics represent a rational approach to treatment of these metabolic abnormalities.

Recognised more recently, features of Resistance to Thyroid Hormone due to defective TRα2 (RTHα2) include growth retardation, neurodevelopmental delay, skeletal dysplasia and constipation, but with near-normal thyroid function tests. The cardiovascular manifestations of this disorder include bradycardia and lower blood pressure; following thyroxine therapy, changes in these parameters and cardiac indices are blunted, reflecting myocardial resistance to hormone action. The divergent phenotypes of RTHβ and RTHα highlight the relative importance of α and β receptor subtypes in mediating TH action in myocardium and other tissues.

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Cardiovascular actions of novel Thyroid Hormone metabolites

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Thyroid hormone (TH) is one of the key players in modulating cardiovascular function. The hormone increases heart rate and force of contraction by modulating cardiac gene expression, thereby providing a molecular explanation for the clinical correlation between hyperthyroidism and cardiovascular mortality. The talk will present current aspects of cardiovascular function mediated by newly discovered TH metabolites. Recent studies have shown that a single injection of 3-iodo-L-thyronamine (3-T1AM), a decarboxylated and detodinated TH derivative, leads to rapid decreases in heart rate and cardiac output. Although 3-T1AM is rapidly converted to several metabolites in vivo, the strong acute pharmacological responses of bradycardia and negative inotropy were solely attributed to 3-T1AM, leaving potential contributions of downstream products untested (e.g. 3-thiodiiodothyroacetic acid or N-acetyl-3-T1AM (NAc-3-T1AM)). Our studies revealed that TAI, the main degradation product of 3-T1AM, lacks any cardiovascular effects in mice, and thus constitutes an important inactivation product of 3-T1AM. However, NAc-3-T1AM, which is produced in liver and WAT from 3-T1AM, significantly increases heart rate and blood pressure in mice and directly enhances contractility of primary cardiomyocytes. Both effects are blocked by the β-adrenergic antagonist timolol maleate, demonstrating that the actions of NAc-3-T1AM on cardiomyocytes require β-adrenergic receptors. Based on our findings, we identify NAc-3-T1AM as a unique endocrine TH metabolite, providing a previously unknown link between liver, WAT and cardiovascular function.

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Endocrinology of ageing men

Abstract unavailable.

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Osteoporosis is considered a postmenopausal disease. Nevertheless, about one out of three of all hip fractures occur in elderly men. Hip fractures in elderly men are also associated with considerable morbidity as well as excess mortality. However, the majority of men suffering from senile osteoporosis are still undiagnosed and undertreated. In 2012 the endocrine society has therefore formulated practical clinical guidelines for the diagnosis as well as treatment of osteoporosis in men.

During this presentation, a clinical case history will be discussed and the practical use of these endocrine society guidelines illustrated. Similar to postmenopausal women, dual energy X-ray absorptiometry (DXA) should be used in order to diagnose osteoporosis in elderly men at risk for osteoporosis. In line with this recommendation, elderly men should have DXA screening following fractures. Some controversies with respect to use of DXA in men still exist with respect to reference values (male or female) as well as site of evaluation (femoral neck only or also, total hip and/or lumbar spine). The use of different diagnostic criteria for male osteoporosis may also identify different numbers of elderly men that are candidates for drug treatment. Secondary osteoporosis should also excluded in elderly men clinically as well as by laboratory testing Laboratory evaluation as proposed by the Endocrine society includes the measurement of serum testosterone. Besides prolonged use of glucocorticoids and alcohol excess, male hypogonadism remains one of the important cause of secondary osteoporosis. Unfortunately, recent studies show that even the majority of men with androgen deprivation still do not receive pharmacological treatment. The same holds true for men that experienced a hip fracture. Pharmacological treatment modalities for elderly men are similar to those used in postmenopausal women despite the limited number of studies in men that have used fractures as an endpoint. Men with low or borderline testosterone with a high fracture risk should also receive pharmacological treatment that prevent against fractures.

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Beyond Phosphorus: multiple actions of FGF23

Fibroblast growth factor 23 (FGF23) has rapidly become the third key player of phosphate/calcium metabolism in the two ‘old’ PTH and vitamin D. FGF23 is a protein synthesized by osteocytes that has three main effects: hypophosphatemia (through an inhibition of phosphate reabsorption in the proximal tubule), decreased PTH levels and decreased 1-25 OH2 levels (through an inhibition of 1α-hydroxylase and an activation of 24 hydroxylase activity in the kidney). Off-targets of FGF23 have also been demonstrated, notably on cardiomyocytes and monocytes. The links between iron metabolism and FGF23 on one hand, and between FGF23 and bone mineralization on the other hand, seem also of importance, although still under investigation. The single-pass transmembran Klotho protein, an anti-aging protein, is required in vivo for FGF23-mediated receptor activation, at least for its renal effects. In human diseases, FGF23 can be deregulated, either in genetic diseases, either in acquired diseases. Four groups can be distinguished: diseases with primary increase of FGF23 levels (e.g., hypophosphatemic rickets or tumor-induced osteomalacia), diseases with primary decrease of FGF23 levels (e.g., hyperparathyphrmatemic tumoral calcinosis), diseases with secondary increase of FGF23 levels (e.g., chronic kidney disease, CKD), and diseases with secondary decrease of FGF23 levels (e.g., VDR deficiency leading to vitamin D-resistant rickets).

This talk will give an overview of these recent data of phosphate/calcium physiology, as well as a description of the clinical conditions associated with FGF23 deregulation. As a conclusion, the future therapeutic perspectives in the field will be discussed.

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Novel actions of FGF23

Novel mechanisms of central weight regulation

S7.1

Nutritional regulation of hypothalamic inflammation
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Hypothalamic inflammation has been the focus of an increasing number of studies in recent years as it is thought to underlie the pathogenesis of obesity-associated insulin resistance and type 2 diabetes. These studies have also highlighted the role of glial cells in metabolic control, due to the fact that both microglia and astrocytes are involved in central inflammatory processes. High fat diet (HFD)-induced obesity has been the most commonly used model for the analysis of this phenomenon, with the diet itself shown to play an important role as hypothalamic inflammation can occur even before significant weight gain is observed. Indeed, fatty acids (FAs) can directly activate glial cells and trigger neuroinflammation. However, this response differs depending on the FA involved, with some FAs possibly being protective. Moreover, not all obesity is induced by HFD intake. The hypothalamic inflammatory/glial response in animals that are obese or overweight due to genetic causes, early nutritional manipulations or high carbohydrate diets differs from that seen in HFD-induced obesity. This talk will focus on the advances in our understanding of the metabolic signals involved in hypothalamic inflammation/glialosis and how this might influence the development of secondary complications such as insulin and leptin resistance.

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S7.2

Regulation of hypothalamic development by maternal nutrition
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In light of the ever-increasing incidences of obesity and T2DM, development of novel therapeutic or preventative measures to combat these epidemics is of utmost importance. Identification of a causal relationship between an altered maternal metabolic homeostasis and an increased propensity for the unborn child to develop metabolic disorders throughout lifetime has shifted considerable amount of attention towards understanding the underlying cellular and molecular alterations. However, despite the multitude of studies already carried out in this field of research, to date we still know very little about the developmental alterations responsible for the increased propensity towards an impaired regulation of energy homeostasis.

By employing a thorough and physiological maternal high-fat diet (HFD) feeding paradigm in mice, we could demonstrate that nutritional and hormonal alterations specifically during lactation predispose the offspring for obesity and impaired glucose homeostasis. These metabolic defects are associated with malformations of the hypothalamic melanocortin circuitry in the offspring. Whereas the number and neuropeptide expression of anorexigenic proopiomelanocortin (POMC) and orexigenic agouti-related peptide (AgRP) neurons, electrophysiological properties of POMC neurons and posttranslational processing of POMC to the active neurotransmitter α-MSH remain unaffected in response to maternal HFD-feeding during lactation, the formation of POMC and AgRP projections to hypothalamic target sites is severely impaired. Moreover, abrogating insulin action in POMC neurons of the offspring prevents altered POMC projections specifically to the preautonomic paraventricular nucleus of the hypothalamus, restores pancreatic parasympathetic innervation and improves glucose-stimulated insulin-secretion in response to maternal overnutrition.

Taken together, these experiments reveal a critical developmental period of particular vulnerability towards altered maternal metabolic homeostasis. An abnormal developmental environment during exactly this period impairs hypothalamic neuronal projections at least in part by abnormal neuronal insulin signaling and thereby contributes to the increased propensity to develop obesity and impaired glucose homeostasis.

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S7.3

Hypothalamic tanyocytes in metabolic regulation
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The survival of an organism relies on its ability to promptly, effectively and reproducibly communicate with brain networks that control food intake and energy homeostasis. To achieve this, circulating factors of hunger and satiety reflecting nutrient availability must cross the blood-brain barrier (BBB) to reach effectors neurons. A defect in this process invariably leads to uncontrolled body weight. Here we will discuss the key role played in this process by a peculiar type of glial cells named tanyocytes, which have their cell bodies lining the floor of the third ventricle and their endfeet contacting the pial surface of the brain. Recent studies indeed suggest that tanyocytes, besides regulating hypothalamic BBB plasticity according to nutrient states, capture metabolic signals such as leptin from the bloodstream and transport them towards their cell body for release into the cerebrospinal fluid. Blockade of this conduit for peripheral metabolic factors into the brain of obese individuals is thought to contribute to the pathophysiology of central hormonal resistance.

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The endocrine gut (Endorsed by Endocrine Connections)

S8.1

Gut microbiota and incretins
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The distal gut harbours microbial communities that outnumber our own eukaryotic cells. Over the last 15 years, our work has been devoted to examine the way by which gut microbiota interacts with nutrients and host physiology. We and others have suggested that cross-talks between gut microbiota and the host cells contribute to the regulation of energy, glucose and lipid homeostasis. We described the concept of metabolic endotoxemia (increase in plasma LPS levels) as one of the triggering factors leading to the development of the metabolic inflammation and insulin resistance. Following this discovery, we found that the major factor involved in the development of metabolic endotoxemia observed upon obesity is related to the gut barrier function. Bacterial metabolism of nutrients in the gut is able to drive the release of bioactive compounds (including short-chain fatty acids or lipid metabolites), which interact with host cellular targets to control energy metabolism and immunity.

We found in both rodents and humans that prebiotics, administration changed gut microbiota composition and activity. In rodents, we found that specific change in the gut microbiota composition improves glucose tolerance, via GLP-1 dependent mechanisms and gut barrier via GLP-2 dependent mechanisms. More specifically, we found that prebiotics increased i-cells number and associated parameters (intestinal proglucon mRNA expression, plasma GLP-1 and 2 levels).

Thus, although the clear mechanisms involved in the bacteria-host interactions are still under investigation, we found that the gut microbiota control enteroneuroendocrine functions and cell differentiation.

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Disclosure
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Role of HSD17B1 in the activation of the sex steroids is also supported by endometriosis, being one of the mechanisms promoting the growth of the lesions in the endometrium. This results into an altered estradiol/estrone balance in the target tissues. So far, among the various HSD17B enzymes, the expression of HSD17B1, HSD17B2, HSD17B3, HSD17B5 (AKR1C3) and HSD17B6 is necessary to mimic their target tissue concentrations in several physiological and pathophysiological settings. Accordingly, among the other steroid metabolizing enzymes, the expression of HSD17B1 in cholesterol synthesis, and HSD17B12 and HSD17B13 KO mice have predicted also other metabolic roles for several other HSD17B enzymes, and thus, a critical evaluation of physiological role of all HSD17B-enzymes in vivo is essential. For example, HSD17B7 KO mice showed a role for the enzyme in cholesterol synthesis, and HSD17B12 and HSD17B13 KO mice indicated a role of the enzymes in lipid metabolism. In conclusion, novel HSD17B-enzyme dependent pathways for sex steroid synthesis and metabolism are emerging at target tissues, and provides new possibilities for the treatment of sex steroid-dependent diseases by HSD17B-inhibitors.

Disclosure

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S8.2

Abstract unavailable.

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S8.3

Stimulation of incretin secreting cells
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In light of the ever-increasing incidences of obesity and T2DM, development of novel therapeutic or preventative measures to combat these epidemics is of utmost importance. Identification of a causal relationship between an altered maternal metabolic homeostasis and an increased propensity for the unborn child to develop metabolic disorders throughout lifetime has shifted considerable amount of attention towards understanding the underlying cellular and molecular alterations. However, despite the multitude of studies already carried out in this field of research, to date we still know very little about the developmental alterations responsible for the increased propensity towards an impaired regulation of energy homeostasis.

By employing a thorough and physiological maternal high-fat diet-(HFD) feeding paradigm in mice, we could demonstrate that nutritional and hormonal alterations specifically during lactation predispose the offspring for obesity and impaired glucose homeostasis. These metabolic defects are associated with malformations of the hypothalamic melanocortin circuitry in the offspring. Whereas the number and neuropeptide expression of anorexigenic proopiomelanocortin (POMC) and orexigenic agouti-related peptide (AgRP) neurons, electrophysiological properties of POMC neurons and posttranslational processing of POMC to the active neurotransmitter α-MSH remain unaffected in response to maternal HFD-feeding during lactation, the formation of POMC and AgRP projections to hypothalamic target sites is severely impaired. Moreover, abrogating insulin action in POMC neurons of the offspring prevents altered POMC projections specifically to the preautonomic paraventricular nucleus of the hypothalamus, restores pancreatic parasympathetic innervation and improves glucose-stimulated insulin-secretion in response to maternal overnutrition. Taken together, these experiments reveal a critical developmental period of particular vulnerability towards altered maternal metabolic homeostasis. An abnormal developmental environment during exactly this period impairs hypothalamic neuronal projections at least in part by abnormal neuronal insulin signaling and thereby contributes to the increased propensity to develop obesity and impaired glucose homeostasis.

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S9.1

Steroid hormone action in target tissues
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Recent data from us and others have evidently shown that steroid metabolism at the target tissues is a key determinant regulating the availability of high affinity ligands for steroid receptors. Thus, the serum concentrations of the steroids do not necessary mimic their target tissue concentrations in several physiological and pathophysiological settings. Accordingly, among the other steroid metabolizing enzymes, the expression of hydroxysteroid dehydrogenase- (HSD17β) enzymes catalyzing the conversion between 17-keto and 17-hydroxysteroids are expressed in various sex steroid target tissues. So far, among the various HSD17β enzymes the expression of HSD17β1, HSD17β2, HSD17β3, HSD17β5 (AKR1C3) and HSD17β6 has shown the strongest association with steroid metabolism in both preclinical models and clinical specimens. HSD17β1 and HSD17β2 enzymes are the ones with the strongest association with altered estrogen metabolism, and are, for example, differentially expressed in endometriosis lesions and in the eutopic endometrium. This results into an altered estradiol/estriol balance in the endometriosis, being one of the mechanisms promoting the growth of the lesions. Role of HSD17β1 in the activation of the sex steroids is also supported by multiple phenotypic alterations in the transgenic mice expressing the human HSD17β1, as well as by the data obtained in the HSD17β1 knockout (KO) mice. Similarly to that of endometriosis, novel routes for the local sex steroid synthesis in the castration resistant prostate cancer have been identified, and the strong intra-tumor androgen production is associated with up-regulation of HSD17β5 and HSD17β6 expression. However, especially the phenotypes of the KO mouse models have predicted also other metabolic roles for several other HSD17β enzymes, and thus, a critical evaluation of physiological role of all HSD17β-enzymes in vivo is essential. Hence, HSD17β7 KO mice showed a role for the enzyme in cholesterol synthesis, and HSD17β12 and HSD17β13 KO mice indicated a role of the enzymes in lipid metabolism. In conclusion, novel HSD17β-enzyme dependent pathways for sex steroid synthesis and metabolism are emerging at target tissues, and provides new possibilities for the treatment of sex steroid-dependent diseases by HSD17β-inhibitors.

Disclosure

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S9.2

Steroid sulphatase and colon cancer
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Although not normally considered an oestrogen responsive tissue, compelling evidence now exists suggesting that the colon is responsive to oestrogenic effects. Results from the Women’s Health Initiative demonstrated that post-menopausal women taking oestrogen and progestins as hormone-replacement therapy (HRT) had a 40% reduction in developing colorectal cancer (CRC). Intriguingly, patients taking oestrogen supplements at the time of CRC diagnosis presented a much more advanced disease stage. Thus, oestrogens are initially protective against CRC, but once developed oestrogens may drive CRC proliferations. Therefore, the pre-receptor metabolism of oestrogens, namely through steroid sulphatase (STS) and the 17β-hydroxysteroid dehydrogenases (17βHSDs), and the oestrogen receptor status of colonic tissue, most likely influence the incidence and subsequent proliferation of CRC.

This presentation will examine the current evidence in support of oestrogenic effects on CRC initiation and development. It will highlight the importance of the peripheral synthesis of oestrogens by STS and 17βHSDs, and how this relates to oestrogen receptor status and proliferation.

Disclosure
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S9.3

Thyroid and autoimmunity
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The autoimmune regulator protein (AIRE) is a critical component of thymic education which leads to immune tolerance. Its recent detection in extrathyroid tissues has prompted inquiry into potential roles for this protein beyond the thymus. We have reported detecting AIRE in circulating CD34+ fibrocytes, monocyte progenitor cells that are involved in tissue reactivity and remodeling. These fibrocytes have been detected in orbital connective tissue from individuals with thyroid autoimmunity.
with thyroid associated ophthalmopathy and in thyroid tissue from patients with Graves’ disease. Further, fibrocytes express functional TSH receptor, thyroglobulin, sodium iodide symporter, and thyroperoxidase. We therefore interrogated these cells for the expression of AIRE and found that both full length and truncated forms of the protein could be detected. When AIRE expression was knocked down with specific targeting siRNAs, levels of all four thyroid associated proteins were substantially reduced. Analysis of fibrocytes from an individual with APS1 disclosed reduced levels of these proteins as well. These findings suggest that AIRE may play an important role in the expression of thyroid autoantigens outside the thyroid. It is possible that AIRE dependent expression of thyroid antigens by fibrocytes may be involved in the manifestations of Graves’ disease such as thyroid associated ophthalmopathy.

promising health-supporting measure. The talk will raise the awareness for this topic and stimulate a discussion on the respective pros and cons.

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Hot topics and IESP symposia

$S11.1$

X-linked acro-gigantism (X-LAG): a new form of infant-onset pituitary gigantism

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Introduction

Pituitary gigantism is a rare disorder caused by GH-secreting lesions. Aim

We studied gigantism for genetic defects. Methods

We performed genome-wide analyses in 46 patients with gigantism and 248 patients with acromegaly. Results

We detected a novel microduplication at chromosome Xq26.3 in two unrelated kindreds and 13 sporadic cases of novo. All patients had disease onset before five years of age and presented with mixed GH/prolactin-secreting macroadenomas and/or hypoplasia. All sporadic cases harbored non-recurrent duplications, whereas familial cases inherited the duplications from their mothers. Breakpoint junctions revealed microhomology, suggesting a replicative mechanism for their formation. Patients shared a common duplicated region of ~500 kb containing four protein-coding genes, of which only GPR101, a G-protein coupled receptor (GPCR) that activates cAMP signaling, was consistently over-expressed in patients’ pituitary lesions. Low GPR101 expression levels were seen in non-duplicated GH-secreting tumors and in most normal adult human tissues, including the pituitary. On the contrary, high expression was observed in human fetal pituitary. Adult pituitaries of both rhesus monkey and rat expressed GPR101 but in different cell types. In the developing zebrafish embryo a strong and brain-specific expression was seen. Conclusions

We describe a new genomic disorder caused by Xq26.3 microduplications (X-LAG for X-linked Acro-Gigantism) and characterized by early-onset gigantism. This syndrome is likely caused by a derepression of GPR101, a dosage-sensitive GPCR that activates the cAMP pathway, whose mitogenic effects in pituitary somatotropes are well established. The brain is the major site of GPR101 expression across different species, although divergent species- and developmental stage-specific expression patterns are evident, especially concerning the pituitary. These differences might reflect the very different growth, development and maturation patterns among species. GPR101 may also be mutated in adult patients with acromegaly.

$S10.2$

Dissecting the function of autoimmune regulator (AIRE)

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AIRE gene is defective in autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) disease. The disease usually starts in early childhood and is characterised by progressive autoimmune destruction of most endocrine and non-endocrine organs and, in addition, mucocutaneous candidiasis. An important characteristic is the presence of autoantibodies against multiple defined antigens. In most cases, these are tissue-specific proteins with important functions in the affected tissues and are identical to the self-antigens found in more common isolated autoimmune disorders such as type 1 diabetes and Addison’s disease. AIRE is expressed in the thymus by medullary thymic epithelial cells, which express hundreds of tissue-specific antigens to eliminate self-reactive T cell clones during a process called negative selection. AIRE mutations result in defective expression of these autoantigens, ultimately causing a failure in negative selection and subsequent survival of self-reactive T cells. The exact mechanisms by which AIRE functions remain unclear. The presentation discusses recent findings in AIRE function and their implications to APECED pathogenesis.

Disclosure

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$S10.3$

Thyroid, selenium and autoimmunity

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The trace element selenium (Se) is unevenly distributed in our earth’s crust causing regional differences in soil Se concentrations. Soil Se directly affects plant Se content and thereby animal and human Se intake. Besides intake, the plant Se content and thereby animal and human Se intake. The actual health status and genotype modify Se metabolism and expression of defined antigens. In most cases, these are tissue-specific proteins with important functions in the affected tissues and are identical to the self-antigens found in more common isolated autoimmune disorders such as type 1 diabetes and Addison’s disease. AIRE is expressed in the thymus by medullary thymic epithelial cells, which express hundreds of tissue-specific antigens to eliminate self-reactive T cell clones during a process called negative selection. AIRE mutations result in defective expression of these autoantigens, ultimately causing a failure in negative selection and subsequent survival of self-reactive T cells. The exact mechanisms by which AIRE functions remain unclear. The presentation discusses recent findings in AIRE function and their implications to APECED pathogenesis.

Disclosure

This work was supported by the Estonian Research Council.

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Endocrine Abstracts (2015) Vol 37
Advances in phaeochromocytoma diagnosis and management (Endorsed by the European Journal of Endocrinology)

S12.1

Update on genetics of phaeochromocytoma/paraganglioma
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Phaeochromocytomas (PCC) and paragangliomas (PGL) are rare neuroendocrine tumours, located in the adrenal medulla (PCC) and in the intra-abdominal, thoracic or head and neck paraganglia (PGL). They have the highest heritability of all human neoplasms being a good example of diseases with underlying genetic heterogeneity. In this regard, at least 40% of PCC/PGL patients carry a germline mutation in one of the 16 genes described so far as related to the disease. In addition to the complexity of the genetics of PCC/PGL, we need to consider the role of somatic mutations, which to date, have been identified at least in 20–30% of tumors. The latter have been observed to occur not only in the same genes involved in heritable susceptibility, but also in new ones, which have thus recently emerged as key players in the sporadic presentation of these diseases. Despite of the increasing proportion of patients who have an already explained by germline or somatic genetic defects, there are still patients with clinical indicators of hereditary disease (i.e. familial antecedents, multiple tumors and/or young age) without a molecular diagnosis, which are being actively investigated. Genomic characterization has provided a robust way not only to identify molecular events associated with specific genotypes, but also diagnostic and prognostic markers. In fact, the new approaches have been responsible for the explosion of knowledge the scientific community is facing. In this regards, most of the latest PCC/PGL genes identified have been discovered after an integrative approach involving transcriptome, mnrnue and melomyelo profiling and next generation sequencing. The talk will review clinical features related to each of the PCC/PGL genes known so far, as well as new findings that point to the Krebs cycle genes as strong candidates to explain additional phaeochromocytoma or paraganglioma cases.

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S12.2

Current imaging of pheochromocytoma/paraganglioma
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After establishing a biochemical diagnosis, pheochromocytomas and paragangliomas can be localized using different imaging modalities. Appropriate imaging is critical for primary tumor localization, the detection of multiple primary tumors and the detection of metastases. This will guide the optimal choice between curative surgery and palliative treatment options.

First line anatomical imaging modalities for pheochromocytoma and paraganglioma imaging include computed tomography (CT) or magnetic resonance imaging (MRI). The specificity of these techniques is limited, however. Functional imaging is complimentary to anatomical imaging and provides specific information about the tumor’s functional characteristics. Nuclear medicine scanning techniques include planar scintigraphy, single-photon emission computed tomography (SPECT) and positron emission tomography (PET). The most widely used radiotracers for pheochromocytoma and paraganglioma scintigraphy are (123I)-labeled metaiodobenzylguanidine (123I-MIBG) and 111In-DTPA-pentetrotide scintigraphy. They have long been considered as the ‘gold standard’ modalities. However, several studies have demonstrated the limitations of using 123I-MIBG scintigraphy alone in the staging of hereditary and metastatic pheochromocytoma/paraganglioma. The use of 123I-MIBG may lead to significant underestimation of metastatic disease. Novel PET tracers have been proven to be very useful for the functional imaging of pheochromocytomas and paragangliomas. These include 6-(18F)-fluorodopamine (18F-FDA), 6-(18F)-fluoro-3,4-dihydroxyphenylalanine (18F-DOPA) and 2-(18F)-Fluoro-2-deoxy-D-glucose (18F-FDG). The performance of the different functional imaging modalities is largely determined by tumor location (adrenal pheochromocytoma and extra-adrenal paraganglioma versus head and neck paraganglioma), benign versus metastatic disease and the underlying hereditary syndrome. The main purpose of 123I-MIBG or somatostatin receptor based scintigraphy in a patient with metastases is to determine if internal targeted radiotherapy is an appropriate treatment choice. Current recommendations regarding the optimal functional imaging strategy for these tumors are made available as part of the Endocrine Society clinical practice guideline on pheochromocytoma and Paraganglioma. Precise identification of the clinical context and genetic status of patients enables personalized use of functional imaging modalities.

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S12.3

Outcome of adrenal sparing surgery in heritable pheochromocytoma: the example of multiple endocrine neoplasia type 2
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With the early management of medullary thyroid carcinoma, multiple endocrine neoplasia type 2 has become an example of chronic disease with prolonged follow-up to look for pheochromocytoma diagnosis and appropriate management. In any genetic disease where pheochromocytoma can happen bilaterally, the surgery has long been based on bilateral adrenalectomy (even in the presence of a single pheochromocytoma), and as a consequence on a life long treatment for adrenal insufficiency. Progress has then been made by choosing unilateral adrenalectomy in case of unilateral pheochromocytoma, which now makes sense. Adrenal sparing surgery is probably another step in trying to improve the patients'
overall quality of life. It is a valuable option well described in patients with phaeochromocytoma and Von Hippel Lindau’s disease. Determining the interest of such a therapeutic approach implies to take into account the risk of recurrence, in comparison with the gain in terms of adrenal function. Moreover, assuming this risk of recurrence implies to characterize the potential of malignancy of hereditary phaeochromocytoma, considering that already medullar hyperplastic tissue will remain after surgery. Data on MEN2 patients are scarce in the literature, usually based on a low number of patients, or a short-term follow-up, and this might explain why this approach is still not considered as the gold standard (when technically do-able).

Based on a large international consortium collecting data on 1210 patients with multiple endocrine neoplasia type 2, including more than 500 with phaeochromocytoma, we determined the outcome of patients with adrenal sparing surgery in comparison with classical adrenalectomy. Our results emphasized the low rate of adrenal insufficiency, and a relatively low risk of recurrence after a median follow-up of 10 years after adrenal sparing surgery. Interestingly, the rate of recurrence was comparable in patients with classical adrenalectomy, whereas, as expected, the rate of adrenal insufficiency was highly superior with the classical approach. Adrenal sparing surgery is thus clearly a valuable therapeutic option, provided a prolonged and regular follow-up can be maintained (Castinetti et al., Lancet Oncology, 2014).

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New concepts in Vitamin D research

Abstract unavailable.

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Clinical consequences of low vitamin D status

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While there is still considerable debate as to what circulating 25-hydroxyvitamin D (25(OH)D) concentration may best represent low vitamin D status, it is clear that there is substantial evidence that the prevalence of vitamin D deficiency (serum 25(OH)D < 25/30 nmol/l) and inadequacy (< 50/75 nmol/l) is moderate and high respectively, across Europe. This has significant implications for human health throughout the lifecycle and may impact on healthy growth and development as well as successful aging for current and possibly future generations. The last two decades has seen an enormous increase in the number of peer-reviewed publications which describe associations between vitamin D status and non-skeletal health outcomes, many of which contribute majorly to the disease burden in Europe and beyond. These are in addition to the traditionally accepted key role for vitamin D in calcium metabolism and skeletal health. This presentation will summarize recent information on the prevalence of low vitamin D status in Europe and wider to provide a perspective. It will also very briefly highlight the impact of methodological considerations in relation to measuring vitamin D status. It will then overview the current and emerging potential health and disease consequences of low vitamin D status, along with some indication of the underpinning evidence-base, where possible. The presentation will finish by highlighting current guidelines for addressing low vitamin D status in patient care but also explore possible strategies by which vitamin D status at population-level might be improved. Prevention of low vitamin D status in patient groups and the general population should pay dividends to the European health-care systems.

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Adipose tissue as an endocrine organ (Endorsed by Endocrine Connections)

Adipose tissue turnover in humans

Kirsty Spalding
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Owing to the increase in obesity, life expectancy may start to decrease in developed countries for the first time in recent history. In humans the generation of fat cells (adipocytes) is a major factor behind the growth of adipose tissue during childhood. The factors determining the fat mass in adults, however, are not fully understood. Increased fat storage in fully differentiated adipocytes, resulting in enlarged fat cells, is well documented and thought to be the most important mechanism whereby fat depots increase in adults. Using a recently developed method, which is based on the incorporation of 14C from nuclear bomb tests into genomic DNA and molecules, we can now also analyse the turnover of adipocytes, their progenitor cells and lipid stores. Results from studies looking at adipocyte and lipid turnover in adult humans, in health and pathology, will be discussed. Understanding the dynamics of adipocyte and lipid turnover may shed new light on potential treatments for obesity.

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FGF1 and PPARγ in the Adipocyte

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Survival requires the ability to adapt to cycles of feast and famine, yet the underlying mechanisms to maintain metabolic balance during extremes of nutrient excess remain poorly understood. We recently discovered that the classic growth factor FGF1 is induced in white adipose tissue (WAT) in response to high-fat-diet (HFD) and repressed during fasting, pointing to an unexpected metabolic function. Thus, FGF1 participates in both fed and fasted-state responses. In WAT, FGF1 is induced by HFD through a PPAR-γ dependent mechanism and thus is also responsive to PPARγ dependent drugs such as Actos and Avandia. Mice with a deficiency in FGF1, when challenged with a HFD, develop an aggressive diabetic phenotype, resulting from adipose that is unable to expand, which progressively becomes inflamed, fibrotic and necrotic and is simply unable to adapt to nutrient stress.

As loss of FGF1 by knockout results in a diabetic phenotype, we speculated that increasing FGF1 levels by direct injection in diabetic mice, could potentially have anti-diabetic effects. As a proteoglycan binding protein, endogenous FGF1 is normally locally restricted. Upon ‘endocrinization’ of FGF1 by simple injection into the body of obese diabetic mice we found potent glucose lowering and insulin sensitizing effects. Thus, more that 30 years after its discovery as a growth factor, ‘endocrinization’ of FGF1 in a diabetic mouse, uncovers a potent yet hidden anti-diabetic phenotype.
Glucocorticoids (GCs) have physiological actions in almost all tissues, classically mediated by the GC receptor. The potent effects of GCs upon metabolic phenotype are best exemplified in patients with circulating GC excess (Cushing’s syndrome), who develop central (visceral) obesity, insulin resistance, myopathy, hypertension and in some cases overt type 2 diabetes (T2DM) and non alcoholic fatty liver disease (NAFLD). GCs are one of the most frequently prescribed class of medication, with 2–3% of UK and US populations currently receiving GC therapy. The clinical efficacy of GC therapy is not in doubt, but their ‘cushingoid’ side effects create significant morbidity and mortality and current prevention strategies to reduce the adverse metabolic consequences are limited. Tissue-specific availability of GC to bind and activate the GC receptor is controlled by a series of pre-receptor regulatory enzymes. 11β-hydroxy-steroid dehydrogenase type 1 (11β-HSD1) regulates the active GC cortisol from inactive cortisone (corticosterone and 11-dehydrocorticosterone respectively in rodents) in adipose tissue, liver and muscle. Indeed, changes in GC availability, notably in adipose tissue, contribute significantly to the development of an adverse metabolic phenotype. Genetic and pharmacological inhibition of 11β-HSD1 in rodent and clinical studies improves the metabolic profile in obesity and T2DM models. This presentation will address how 11β-HSD1 contributes to promoting the unwanted metabolic aspects of GC excess and the ‘cushingoid’ phenotype often seen in patients taking GC therapy, with particular emphasis on adipose tissue specific GC effects. We propose that 11β-HSD1 inhibition may offer protection from a deleterious metabolic profile in the context of the GC excess state.

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Puberty: new mechanisms

Epigenetics of Female Puberty
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A prevailing concept regarding the mechanism controlling the timing of puberty proposes that GnRH release from the hypothalamus increases at puberty due to a loss of transsynaptic inhibition, accompanied by an increase in neuronal/glial excitatory inputs to GnRH neurons. Without negating the importance of this intercellular communication process, recent evidence suggests that a critical inhibitory/excitatory Yin-Yang mechanism regulating the advent of puberty is epigenetic in nature and affects the transcriptional activity of neurons involved in stimulating GnRH release (such as kisspeptin neurons). The repressive arm of this mechanism is provided by the Polycomb group (PcG) of transcriptional silencers, which prevents the premature initiation of female puberty by silencing the Kiss1 gene in kisspeptin neurons of the arcuate nucleus (ARC) of the hypothalamus. At the end of juvenile development PcG proteins are evicted from the Kiss1 promoter and the abundance of the PcG-catalyzed, ‘repressive’, histone modification H3K27me3 is reduced. The antagonistic counterpart of PcG-mediated gene silencing is provided by the Trithorax (TrxG) group of transcriptional activators. Like the PcG complex, TrxG genes are expressed in kisspeptin neurons of the ARC. Key TrxG proteins required for the synthesis of ‘activating’ histone marks (histone 3 di- and trimethylated at lysine 4) are recruited to the Kiss1 promoter at the initiation of puberty and this correlates well with an increased abundance of the activating histone marks H3K4me3 and histone 3 acetylated at lysine 9 and 4 (H3K9, 14 ac) at the promoter. Both the PcG and the TrxG systems are, in turn, regulated by upstream repressors. Whereas PcG gene expression is inhibited by members of the POK (for POZ and Krüppel) family of transcriptional regulators, TrxG action is attenuated by zinc finger (ZNF) proteins that facilitate the demethylation of H3K4me2 via recruitment of a specific lysine demethylase (KDM) family member to the Kiss1/T1AC promoters. The presence of this tight system of epigenetic regulation in Kiss1/TAC3 expressing neurons of the ARC suggests that a switch from epigenetic repression to activation within these neurons underlies the developmental process by which GnRH release is first kept in check before puberty, and then increases by late juvenile development to bring about the pubertal process. (NSF grant 1121691)

Disclosure
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GnRH development and function: lessons from semaphorins
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This talk summarizes recent studies analysing the contribution of specific guidance molecules named semaphorins in the development and adult function of gonadotropin-releasing hormone (GnRH) neurons. In vertebrates, the GnRH decapeptide regulates the secretion of luteinizing hormone and follicle stimulating hormone, which govern puberty onset, gametogenesis, and estrous cycling, from anterior pituitary gonadotropes. During embryonic development, these cells originate from the nasal placode and migrate to the hypothalamus apposed to olfactory-vomeronasal nerves.

Alterations either in the development of this system or in the secretion of GnRH are associated with reduction or failure of sexual competence. In order to understand the pathogenesis of human reproductive disorders, it is thus relevant identifying molecular pathways involved in the regulation of the GnRH system. The semaphorin proteins are one of the largest families of guidance cues, contributing to morphogenesis and homeostasis in a wide range of tissue types, including the brain. During embryonic development, several semaphorins are expressed in the olfactory-vomeronasal system and along the GnRH migratory route, prompting several groups of research to study their eventual involvement in the proper development of the GnRH and olfactory systems.

In recent years several studies have started to shed light on the role of semaphorins in the motility, survival and axonal plasticity of GnRH neurons. This talk will review some of these studies, which provided insight into the sophisticated molecular mechanisms that allow for the spatiotemporal control of the responsiveness to semaphorins of developing GnRH neurons. Genetic data are also presented to show that some forms of reproductive disorders in humans are associated with mutations in specific classes of semaphorin family members.

Finally, some emphasis will be put on some recent studies, which started to shed light on the molecular mechanisms responsible for the progression of the estrous cycle in rodents and suggest that this phenomenon relies on the antagonistic effects of two semaphorins whose expression in the median eminence is periodically influenced by circulating sex hormones.

Disclosure
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Genetic regulators of the timing of puberty
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The timing of puberty varies widely between individuals and in girls early puberty timing is associated with higher risks for adult obesity, type 2 diabetes (T2D), cardiovascular disease (CVD), breast cancer and all-cause mortality. Understanding the regulation of puberty timing therefore has relevance to disease pathogenesis as well as developmental and human biology. Large-scale genome-wide association studies have identified robust evidence for more than 100 independent genomic association signals associated with age at menarche, including overlap with genes that are disrupted in rare disorders of puberty. Such findings have implicated RNA-mediated gene silencing, histone regulation of gene activity, and retinoic acid-related nuclear receptors among novel mechanisms that regulate puberty timing. Menarche signals are enriched in imprinted gene regions and three imprinted loci (DLK1/D13S825, MKRN3/MA-GELE2, and KCNK9) demonstrated parent-of-origin specific associations concordant with their known parental expression patterns; these findings indicate parental conflicts over the selective advantages of puberty timing. Recent findings provide evidence for a substantially shared genetic etiology of puberty timing between males and females, and also indicate causal relationships between earlier puberty timing and higher BMI, T2D, and CVD, which are likely mediated by both BMI-related and BMI-independent mechanisms.

Disclosure
This work was supported by the Medical Research Council (Unit Programme number MC_UU_12015/2).

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Pathogenesis of adrenocortical tumours

S16.1

Inherited tumour syndromes and adrenal cancer
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Adrenocortical carcinoma (ACC) is a rare endocrine cancer with a poor prognosis. Roughly 10–15% of all ACCs arise in patients with a predisposition to cancer development due to a germline mutation. Pediatric ACC is a well-described core malignancy of the Li Fraumeni syndrome tumour spectrum. More recently TP53 mutations have also been found in adult ACC patients. In addition recent advances in clinical and molecular genetics have identified additional familial cancer syndromes, such as Lynch syndrome and Carney Complex, contributing to ACC development in adult patients. Familial cancer syndromes can often be identified by obtaining a detailed family and personal history, and finding clues on physical exam. Identifying an underlying germline mutation in a patient with the diagnosis of ACC may impact treatment decisions, and allows for individual strategies for preventive surveillance regarding other associated tumours and for further family cascade screening. Due to the significant prevalence of familial cancer syndromes amongst patients with ACC, we recommend considering genetic counselling and a genetic work-up for all patients with ACC.

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S16.2

Role of steroidogenic factor-1 in the pathogenesis of adrenocortical tumours
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Steroidogenic factor-1 (SF-1, NR5A1) is a transcription factor that plays an essential role in the development of adrenal glands and gonads. Multiple levels of regulation of SF-1 activity is exerted by interaction with cofactors, post-translational modifications and epigenetic gene expression regulation. Our studies involving both cell lines and translational mouse studies showed that an increased SF-1 dosage activates adrenocortical cell proliferation and causes adrenocortical neoplasia. By employing multiple genomic approaches, we defined different levels of regulation in transcriptome, miRNome and more recently on regulome exerted by SF-1 dosage. We identified new functional interactions between SF-1 and neuron-restrictive silencer factor/RE1-silencing transcription factor (NRSF/REST) suggesting that SF-1 has a broader role than initially thought in regulating tissue-specific gene expression programs.

We showed that SF-1 dosage differentially regulates the expression of numerous and distinct genes, involved in a variety of biological processes, suggesting that fine regulation of SF-1 dosage is a critical determinant of its action during adrenal development, function and tumourigenesis.

We identified fetal and adult testis expressed-1 (FATE1), a cancer tests antigen (CTA), as a new dosage-dependent target of SF-1. CTAs are emerging as attractive targets for therapeutic cancer vaccines due to their expression in tumors but not in normal tissues except testis. Our recent studies aim to better understand the role of FATE1 in tumor cellular metabolism, mitochondrial morphology and signaling and in drug resistance, potentially important for the aggressive phenotype of adrenocortical carcinoma.

Our project aims to investigate the involvement of these new SF-1 target genes in adrenal pathophysiology to improve the diagnostic of ACC and in the future to develop innovative strategies for cancer treatment.

Disclosure

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S16.3

miRNA as biomarkers in adrenal cancer?
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MicroRNA (miRNA) are small RNA molecules involved in the posttranscriptional regulation of gene expression. Differential expression of miRNA has been described in several tumours. miRNA expression patterns can be used as markers of malignancy, as prognostic markers and even for the subclassification of tumours. miRNA markers can be especially useful for the diagnosis of tumours whose histological analysis is difficult such as adrenocortical cancer (ACC). Beside tissue miRNA, miRNA are also released into the circulation and these blood-borne circulating miRNA might have great potential as minimally invasive markers of malignancy. Several reports including ours have described potential tissue and circulating miRNA markers of ACC. The applicability of tissue miRNA as biomarkers is further extended due to their stability, and therefore formalin-fixed paraffin embedded tissue blocks can be used for miRNA analysis. Among tissue miRNA markers of malignancy, overexpressed miR-483-5p, the expression difference of miR-503-miR-511 and underexpressed miR-195 are most promising showing high sensitivity and specificity values. Some miRNA markers might be exploited as prognostic markers, including miR-483-5p, miR-195, miR-503 and miR-210. Three studies to date have reported on circulating miRNA profiles in ACC. Overexpressed miR-483-5p, miR-100, miR-181b, miR-210 and miR-34a have been proposed as circulating miRNA markers of ACC. Circulating miR-483-5p and miR-195 might be exploited to distinguish aggressive and non-aggressive cancer forms. There are several technical problems associated with the analysis of circulating microRNAs that need to be overcome for their reliable use. miRNA expression patterns of aggressive and non-aggressive forms of ACC are different as established by next generation sequencing data. In conclusion, both tissue and circulating miRNA are promising biomarkers but most studies included only limited sample sets and there are significant differences among different studies. Sample size extension, the standardization of analytical approaches will be needed to confirm the suitability of miRNA markers in adrenal cancer.

Disclosure

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Diabetes and bone (Endorsed by the European Journal of Endocrinology)

S17.1

Diabetes and osteoporosis – cause for concern?
Peter Vestergaard
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Background

Diabetes and osteoporosis are both frequent conditions, a link may thus put a substantial number of patients at risk of fragility fractures and the consequences of these such as pain, disability, and increased mortality. Skeletal fragility and osteoporosis may represent a hitherto overlooked complication of diabetes in line with say diabetic eye disease, diabetic nephropathy etc.

Findings

An increased risk of fractures has been observed in both type 1 and type 2 diabetes. In type 1 diabetes, a decreased bone density has been observed, while in type 2 diabetes, bone density may actually be increased. A discrepancy seemingly exists between bone density and fracture risk in diabetes, especially in type 2 diabetes. The increase in fracture risk has been observed at the hip, spine, and forearm as well as for overall risk of fractures. Especially the risk of hip fractures seems increased in type 1 diabetes, whereas the increase is less pronounced in type 2 diabetes. Hypoglycemia seems to play a minor role for the occurrence of fractures. The increase in fracture risk seemingly is related to diabetes per se and less so to complications (say falls related to diabetic eye disease).

Conclusions

An increased risk of fractures – in particular hip fractures, which may be associated with significant excess mortality and morbidity – may be present. The increase may be linked to skeletal frailty resulting from metabolic disruptions stemming from impaired glucose metabolism rather than from falls related to hypoglycemia or say reduced eye sight.

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S17.2

Pathophysiology of diabetoporosis
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Both type 1 and 2 diabetes are associated with an increased fracture risk. Whereas in type 1 bone fragility is mostly explained by a lower peak bone mass and low bone turnover state, which is a common feature of several chronic and/or inflammatory diseases starting during growth, in type 2 diabetes there is not necessarily low bone mass, rather a higher aBMD related to overweight/obesity in
Clinical management of fragile bone in type 2 diabetes
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Given the increasing acceptance of increased fracture risk that occurs in patients with type 2 diabetes, a number of strategies need to be considered reflecting the multiple factors underlying the fracture risk. These comprise measures to improve falls risk, the avoidance of treatments that may be detrimental to skeletal health and the use of treatments to maintain or improve bone strength.

Older people with diabetes are at high risk of falls, recurrent falls and fractures. Risks factors for falls in older persons with diabetes include polypharmacy, muscle weakness, previous stroke, motor and sensory neuropathy, poor glycaemic control, hypoglycaemia, insulin use, cognitive dysfunction, orthostatic hypotension, and visual impairment. Lower HbA1c has been associated with higher risk of falls frail elderly people and hip fracture, especially in those treated with insulin. Falls risk should be assessed in all patients as many studies using techniques such as gait, balance, and strength training have shown reduced risk of falls for people with diabetes. No studies have shown a reduction in fracture risk. The significant side effect profile of thiazolidinediones includes concerns over an increase in the risk of fractures. This and other potential side effects has significantly decreased the enthusiasm for their use, despite their potential convenience in older people. The majority of the fractures have occurred in the limbs and guidance suggests that the risk of fracture should be considered in the care of patients, especially female patients, treated with such agents.

The evidence base for the use of agents developed for the treatment of osteoporosis in the setting of increased fracture risk in type 2 diabetes is lacking. The majority of studies have either excluded diabetes directly or indirectly by the requirement of low BMD at study entry. The decrease in bone turnover markers observed in type 2 diabetes raises a question mark over the use of antiresorptive therapies. Furthermore, post-hoc analyses of Phase 3 studies suggest that some anti-resorptive agents are less effective in the presence of a high BMI. In contrast, epidemiological studies suggest that diabetes does not seem to affect the fracture preventive potential of bisphosphonates or raloxifene.

New genetics of pituitary tumours (Endorsed by the European Journal of Endocrinology)
S18.1
A novel role for stem cells in the regulation of turnover in the postnatal pituitary
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Dysfunction in the mechanisms that regulate cell numbers in the pituitary gland can underlie hypopituitarism as well as the generation of tumours. Investigations into how these conditions arise has led to an interest in identifying mechanisms for correct maintenance of endocrine cells throughout life. Currently, the source and identity of signals promoting this maintenance in the postnatal pituitary are not known. We have previously shown that pituitary-specific disruptions in the WNT signalling pathway, a key developmental pathway often perturbed in disease including cancer, can lead to developmental anomalies and tumorigenesis. Here, we provide in vivo evidence that WNT signals promote the generation of new cells in the anterior pituitary. Using genetic lineage tracing in mouse we show that SOX2-expressing cells act as stem cells in vivo, able to differentiate into all hormone-producing lineages and contribute to organ homeostasis during postnatal life. However, SOX2-expressing stem cells are not the sole source of new endocrine cells at these stages, but complement contribution from more committed cell types. We find that committed cells responding to WNT signals are capable of proliferation and provide the majority of organ turnover. Unexpectedly, we uncover that SOX2-expressing stem cells act as critical regulators of this process through secreting WNT ligands promoting proliferation, thus influencing long-term physiological cell turnover in a paracrine manner. This represents a key step towards understanding the mechanisms controlling stimulation of new cell generation in situ, with an impact on future therapies for diseases of the pituitary gland.

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Metabolic dysfunction in PCOS
S19.1
Genetic determinants of metabolic dysfunction in PCOS
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PCOS is a common disorder that is reported to affect 5–7% of women of reproductive age. Although there has been debate about the diagnostic criteria for...
PCOS, hyperandrogenemia/hyperandrogenism, not explained by other causes, is a hallmark of the disorder, and it is included as an essential element in all 'consensus' diagnostic schemes. Studies on cultures of human theca cells derived from normal and PCOS women have demonstrated that PCOS theca secretes greater amounts of androgen than theca tissue or cells from regularly ovulating women. Increased CYP17A1 (I540 17α-hydroxylase/17,20-lyase) gene expression in PCOS theca cells is associated with excess androgen production. Our previous molecular characterization of PCOS theca cells and normal theca cells from multiple individuals by microarray analysis and PCR established that normal and PCOS theca cells have distinctive molecular signatures, suggesting intrinsic (genetic) differences. A major milestone was achieved with the publication of a genome-wide association studies (GWAS) on Han Chinese, which identified eleven loci, including DENND1A, a finding that was subsequently validated in European populations. DENND1A is a clathrin binding protein found in coated pits, and which positions it to modulate cell surface receptor signal transduction. Using cultured human theca cells, we have shown that an isoform of DENND1A, V2, is over-expressed in PCOS theca cells compared to theca cells derived from ovaries of normally cycling women. V2 overexpression in PCOS may be the result of alternative splicing. Forced expression of V2 increases androgen production, and CYP17A1 mRNA in normal theca cells, whereas knock-down of V2 expression reduces androgen secretion and CYP17A1 mRNA in PCOS theca cells. Both humanized monoclonal antibodies against V2, and their Fab fragments, also reduce androgen production and CYP17A1 mRNA when added to cultured PCOS theca cells. DENND1A V2 can be placed into a network of genes identified in the Chinese GWAS that can explain the hyperandrogenemia phenotype of PCOS.

Disclosure
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S19.2
The role of androgens in PCOS-related insulin resistance
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Insulin resistance and androgen excess are the cardinal features of polycystic ovary syndrome (PCOS). The severity of hyperandrogenism and metabolic dysfunction in PCOS are closely correlated but the underlying mechanisms are poorly understood. Aldoketoreductase type IC (AKR1C) is an important source of androgen production (converting androstenedione to testosterone) and we have postulated that it may have a critical role linking androgen metabolism and metabolic phenotype in PCOS.

Ten patients with PCOS, three with insulin resistant (INSR) mutations and ten control patients underwent oral DHEA challenge with concomitant adipose tissue microdialysis. Serum and adipose androgens, and adipose glycerol levels, were sampled every 30 minutes for 4 h. In parallel, adipose androgen generation (measured using LC/MS-MS), was studied using primary cultures of human theca cells, whereas knock-down of V2 expression reduces androgen secretion and CYP17A1 mRNA in PCOS theca cells. Both humanized monoclonal antibodies against V2, and their Fab fragments, also reduce androgen production and CYP17A1 mRNA when added to cultured PCOS theca cells. DENND1A V2 can be placed into a network of genes identified in the Chinese GWAS that can explain the hyperandrogenemia phenotype of PCOS.

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S19.3
Endocrine consequences of childhood cancer treatment
S20.1
Reproductive function in cancer survivors
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With increasing numbers of survivors from cancer at a young age the issue of fertility preservation has assumed greater importance. Female fertility preservation provides significantly different challenges to that for the male. Embryo freezing is now an accepted and well-established procedure in many centres, but is not available for children who do not have a partner. Cryopreservation using vitrification of mature oocytes has become increasingly successful, but requires the patient to go through a course of hormone stimulation and is therefore not appropriate for children and young girls. Ovarian tissue cryopreservation has the potential advantages of preservation of a large number of oocytes within primordial follicles, it does not require hormonal stimulation when time is short, and is appropriate for the pre-pubertal girl. Disadvantages include the need for an invasive procedure, and the uncertain risk of ovarian contamination in hamartological and other malignancies. Ovarian tissue cryopreservation in adult women with later re-implantation has resulted in at least 39 live births worldwide. The number of re-implantations is unknown and this invasive approach to fertility preservation remains unproven and experimental in children and adolescents. The majority of young patients treated for cancer will have a window of opportunity for natural fertility if they survive their original cancer. We have published guidelines for patient selection in young female patients with cancer and in this lecture I will report our practise in a single centre that has offered fertility preservation since 1996 (Wallace et al., Lancet Oncology 2014).

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S20.2
Hypopituitarism in cancer survivors
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Survival rates of childhood cancer have improved markedly and today more than 80% of those diagnosed with a pediatric malignancy will become 5-year survivors. Nevertheless, survivors exposed to cranial radiotherapy (CRT) are at particularly high risk for long-term morbidity, such as endocrine insufficiencies, metabolic complications and cardiovascular morbidity. Deficiencies of one or more anterior pituitary hormones have been described following therapeutic CRT for primary brain tumours, nasopharyngeal tumours, and following prophylactic CRT for childhood acute lymphoblastic leukemia (ALL). Studies have consistently shown a strong correlation between the total radiation dose and the development of pituitary deficits. Further, age at treatment and also time since treatment has strong implications on pituitary hormone deficiencies.

There is evidence that the hypothalamus is more radiosensitive than the pituitary and is damaged by lower doses of CRT. With lower doses of CRT (<50 Gy), the primary site of radiation damage is the hypothalamus and this usually causes isolated GH deficiency (GHD). Higher doses (>50 Gy), as were used in nasopharyngeal carcinomas, may produce direct anterior pituitary damage, which contributes to multiple pituitary deficiencies. The large group of ALL-survivors treated with CRT in the 80-90-ties has now reached adulthood and these survivors were treated mainly with 24 Gy and the vast majority of these patients suffer from GHD. Further, after long-term follow up we have recorded insufficiencies in Prolactin and TSH and proportion of these patients were also ACTH deficient. The more CRT sensitive hypothalamius causes neuroendocrine dysfunction, which means that the choice of GH test is crucial for the diagnosis of GHD.

Swedish Childhood Cancer Foundation.

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Late effects of cancer treatment on cardiovascular risk

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In the last 50 years survival after childhood cancer has dramatically improved. However, childhood cancer survivors (CCS) are at risk for a considerable array of late effects arising from previous anti-cancer therapies. The excess mortality (compared with the general population) in CCS is mostly due to second neoplasms and cardiovascular diseases. Indeed, the cardiovascular system has been recognized as a highly sensitive target for damage by anti-cancer therapies. Early in the study of late effects, the anthracyclines were identified as a cause of late-onset myocardial dysfunction, with a dose-dependent mechanism. Moreover, radiotherapy was widely used in treatment protocols of several paediatric cancer (e.g. Hodgkin disease) but all components of the heart (pericardium, myocardium, valves and conduction system, as well as artery wall) are susceptible to ionizing radiations. Hence it follows that CCS treated with chest radiotherapy have a high risk of coronary artery disease, but also of valvular abnormalities, arrhythmias and stroke. Furthermore, several studies reported that CCS are more likely to have additional risk factors (dyslipidaemia, hypertension, diabetes). CCS, in general, are twice as likely to be hypertensive or diabetic as their siblings, with higher prevalence of these conditions in patients treated with abdominal radiotherapy or bone marrow transplantation. Obesity is a well known late effects in survivors of central nervous system tumours (due to hypothalamic damage or reduced physical activity). In conclusion, CCS need a long-term follow-up to manage this cardiovascular risk, in accordance with the growing evidences on this field and recommendations proposed by international cancer survivorship institutions.

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Secondary cancers in childhood cancer survivors

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Due to marked advances in curative therapy for childhood cancer – mainly the introduction of modern chemotherapy in the 1960s – the 5-year survival rate after childhood cancer has substantially improved over the last few decades from less than 30% in the 1960s to currently over 80%. As a result of these improved survival rates, a large and ever growing number of childhood cancer survivors have reached adulthood. A major concern following treatment of childhood cancer is the increased long-term risk of second primary cancers. Treatment with radiotherapy and – although to a lesser extent – specific chemotherapeutic agents have been associated with an increased risk of developing secondary primary cancers. This presentation will provide an overview of the evidence from previous studies that have investigated the risks of second primary cancers in survivors of childhood cancer. Particular attention will be given to the extent to which the risks of second primary cancer vary by type of childhood cancer and to what extent the risk varies by attained age and time since childhood cancer diagnosis. More survivors are now reaching an age at which in the general population the risk of common cancer increases. This implies that even a small increased risk relative to that observed in the general population could lead to a substantial excess number of survivors of childhood being diagnosed with a second primary cancer. Understanding the long-term risks of second primary cancers is crucial because it provides a basis for counselling long-term survivors, planning future clinical follow-up and deciding on new treatment protocols with the ultimate aim of reducing the risks of developing second primary cancers without compromising the currently achieved 5-year survival rates.

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Thyroid hormone in pregnancy

S21.1

Abstract unavailable.

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Consequences of maternal thyroid dysfunction for offspring

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Treatment of hyperthyroidism with antithyroid drugs has recently been shown to have an effect on MMI/Carbamazepine embryopathy at a specific early window in gestation. This has important implications for management.

There is agreement that untreated overt gestational hyperthyroidism is associated with significant adverse obstetric and fetal/neonatal effects. Although there is also substantial evidence that gestational subclinical hypothyroidism (SCH) is associated with miscarriage, gestational hypertension, preterm delivery and decreased IQ in the offspring, there is a dearth of randomised studies in relation to maternal treatment in pregnancy. In addition there are recent data documenting significant ethnic variation in thyroid function in pregnancy which may affect the calculated incidence of SCH. The associated neuropsychological effects of SCH on the child now include behaviour disorders including ADHD and autism. Moreover, isolated hypothyroxinaemia (IH) is also associated with many of the adverse effects seen with maternal SCH and there is continuing debate as to whether this condition should be treated during gestation. Because of the uncertainties relating to outcomes following L-thyroxine therapy in SCH and IH the question of routine screening for thyroid function in early gestation is still controversial. Published guidelines on thyroid disease and pregnancy in general do not support screening despite the evidence that targeted case finding will miss more than 50% of women with thyroid dysfunction. Results of more randomised studies are awaited but several centres and endocrine societies are already committed to the screening strategy.

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Thyroid hormone in brain development

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Thyroid hormones (T4 and T3) have a major role in brain development, and their deficiencies during critical stages during the fetal and neonatal periods may cause profound intellectual and neuromotor deficits. A particular example is the X-linked Allan-Herndon-Dudley syndrome, caused by mutations of the cellular transporter for thyroid hormone MCT8 (SLC16A2). In this presentation I will first review the pathophysiology of thyroid hormone transport and metabolism in the brain, and the interaction between the main players, i.e., the transporters, the deiodinases, and the nuclear receptors. Then I will review how thyroid hormone (T3) acts at the genomic level by regulating the expression of many genes. In particular I will present recent data from our laboratory using primary mouse cerebrocortical cells in culture that has permitted the identification of primary and secondary gene responses after T3 addition. Genomic data indicate that the role of thyroid hormone is to facilitate the transition from a fetal pattern to a mature or adult pattern of gene expression.

Disclosure

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Beta cell biology
S22.1
Noncoding genome function in pancreas development and disease
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Most genetic mechanisms that are currently known to underlie developmental processes and human diseases are based on the analysis of a very small portion of the genome that encodes for protein-coding sequences. Novel sequence-based technologies, however, have recently disclosed that a major portion of the noncoding genome contains functional regulatory elements. It is thus reasonable to presume that the analysis of such elements can shed new light into developmental and cellular mechanisms, and uncover new causes of human disease. The elucidation of such defects will require knowledge of the genomic location of functional noncoding elements in disease-relevant cell types, as well as an in-depth understanding of how they function. I will present data showing how transcriptional network maps and epigenomics of embryonic pancreatic cells can uncover novel cis-regulatory mechanisms of pancreas development, and will also present findings that use this knowledge to identify genetic causes of Mendelian forms of human diabetes. Further, I will discuss data indicating that non-coding genome variation can also contribute to the susceptibility for common forms of human diabetes.

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S22.2
Novel therapeutic targets in the β-cell
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Metabolic and inflammatory insults contribute to β-cell failure and apoptosis, in part via the generation of reactive oxygen species (ROS). The pancreatic β-cell acquires sensitivity to the damaging actions of pro-inflammatory cytokines during differentiation, but the mechanisms underlying the differentiation-dependent sensitisation is unknown. By mRNA microarray of a cell-model of β-cell differentiation exposed to cytokines we identified a cluster of transcripts involved in metal-ion handling, including the divalent metal transporter DMT-11. Cytokines up-regulated DMT-1 expression and iron import in β-cell-lines and islets. DMT-1 knock-down prevented cytokine-induced β-cell apoptosis. We generated an inducible β-cell specific DMT-1 knock-out (KO) mouse. Islets from these mice were protected from cytokine-toxicity in vitro, and glucose intolerance caused by both low-dose streptozotocin causing an autoimmune islet response but also by high-fat feeding was attenuated in DMT-1 KO mice. For this reason we have investigated whether FFA regulate β-cell and islet DMT-1 expression, iron import and ROS formation, and if DMT-1 KO prevented FFA induced islet secretary failure and apoptosis. The results of these studies will be presented. Elevated iron saturation conferred risk of diabetes development in large population studies. This evidence suggests that pathways regulating iron handling may harbour novel therapeutic targets for anti-diabetic drugs.

References

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S22.3
Novel models of human pancreatic β cells
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Despite intense efforts over the past decades, human pancreatic β cell lines with physiological insulin secretion have not been available. We have developed a robust transplantation model of fetal human pancreases that recapitulates pancreas development and combined such model with integrative lentiviral-mediated gene transfer. This resulted in production of human transgenic pancreases in which dynamic aspects of development can be studied. We thus forced expression of immortalizing transgenes in developing human beta cells and were able to produce the first and only functional human beta cell lines. Importantly, such lines secrete insulin in response to glucose and are able to revert chemically induced diabetes in mice upon transplantation. Furthermore, we derived a conditionally immortalized human pancreatic β cell line using Cre-dependent reversible immortalization. After massive amplification immortalizing transgenes are removed resulting in proliferation arrest and dramatic enhancement of beta cell function. Altogether, these cell lines represent unique tools to study beta cell biology studies, for drug discovery and as preclinical model for cell replacement therapy.

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Adrenal insufficiency: advances in diagnostics and therapy (Endorsed by the European Journal of Endocrinology)
S23.1
How to diagnose adrenal insufficiency in critical illness?
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Critical illness represents a major challenge for the human body where an adequate stress response is indispensable for survival. Concomitantly high cortisol levels are observed and for a long time, an increased activation of the hypothalamic-pituitary-adrenal axis (HPA) was assumed to explain this hypercortisolism. Furthermore, insufficient activation of the HPA-axis during critical illness was described and referred to as ‘relative adrenal insufficiency’ or ‘critical illness-related corticosteroid insufficiency’ (CIRCI). These terms comprise insufficient adrenal cortisol production to match the level of stress due to a malfunctioning of the HPA-axis or a cortisol resistance of the peripheral tissues. Suggested diagnostic criteria were based on a landmark study by Annane et al. who identified a cortisol incremental response of < 9 µg/dl after ACTH-injection and a baseline cortisol level > 34 µg/dl as discriminative for increased risk of death. However, other investigators have not been able to replicate this. Furthermore, it remains debated whether CIRCI should be treated with exogenous glucocorticoids and with which doses. Indeed, randomized controlled studies generated conflicting results. The important lack of knowledge on the pathophysiology of CIRCI currently retains further improvement of diagnosis and treatment of CIRCI.

Recent novel insights have shown that cortisol metabolism was reduced which contributed to hypercortisolism, with limited increased cortisol production. The concomitant low ACTH levels, explained by negative feedback, could lead to an understimulation of the adrenal gland and negatively affect adrenal structure and function, given the crucial role of ACTH for adrenal gland maintenance. Predominantly in the prolonged phase of critical illness this could influence outcomes and explain the increased incidence of adrenal failure in these patients. These findings represented a paradigm shift in our current understanding of HPA-axis regulation during critical illness and will redirect future research, underlining the urgent need for well-designed clinical trials.

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S23.2
Regenerative therapy in autoimmune Addison’s disease
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It is obvious that adrenal cortex is plastic, with adrenal atrophy and functional hypoaldosteronism during exogenous glucocorticoid therapy; yet adrenal hyperplasia and hyperfunction during stimulation from ACTH during Cushing’s disease. This is owing to subcapsular adrenocortical stem cells that regenerate the zones of adult adrenal cortex throughout life. We have performed a series of experimental medicine trials in order to explore the idea that autoimmune Addison’s disease may therefore be remediable. These
studies have used either immunomodulation with B lymphocyte depletion therapy, high-dose ACTH analogue or both, in order to try to modify the natural history of the condition. In summary, there are a proportion of people (~20%) with both newly diagnosed and established autoimmune Addison’s disease who have some degree of residual adrenal function. In a few people we have induced a durable, steroid medication-free remission of Addison’s disease which has lasted from 6 months to as long as 4 years and ongoing. This opens a window for further regenerative medicine strategies to ameliorate adrenal failure in this patient group.

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$S23.3$

Cortisol measured in scalp hair as a monitoring tool for systemic cortisol levels
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In recent years, scalp hair analysis had been successfully introduced as a novel biomarker for long-term cortisol levels. Traditionally used methods to measure cortisol (blood, saliva, urine) are complicated by the circadian rhythm and pulsatile way of cortisol secretion, as well as the influence of acute stress and day-to-day variation. In contrast to these short-term measurements, hair cortisol analysis allows to quantify the average cortisol production for a prolonged period of time ranging from 1 month to several months or even years, depending on the length of the hairs.

Hair analysis provides exciting new opportunities to study the influence of long-term cortisol exposure on a wide range of health outcomes and diseases. In this context, increased long-term cortisol levels have been associated to obesity, metabolic syndrome, cardiovascular diseases, psychiatric diseases and a wide variety of stress-related conditions. Also for endocrine diseases hair cortisol analysis has shown its value. Hair cortisol measurement has been shown to be a convenient, non-invasive tool to diagnose Cushing’s syndrome with high sensitivity and specificity. Evidence is accumulating that this method can also be used for monitoring of hydrocortisone replacement therapy to improve its refinement. As hair grows on average one centimeter per month, scalp hair offers the unique opportunity to create historical timelines of long-term levels of cortisol. This facilitates the measurement of cortisol levels before and after an intervention or event using one single hair sample. In addition, in cases of cyclical Cushing’s syndrome, retrospective hair analysis seems of great value to assist in diagnosing this rare disorder. In conclusion, hair seems a promising matrix to reliably measure cumulative cortisol levels over prolonged periods of time, yielding multiple clinical applications.

Disclosure
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Androgens and disease progression in prostate cancer

$S24.1$

Leveraging circulating DNA studies to identify mechanisms of resistance to CYP17A1 inhibition
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CYP17A1 inhibition with abiraterone is an effective treatment for castration-resistance prostate cancer (CRPC), with significant improvements in survival, radiological progression free survival, pain, skeletal related events and other secondary end-points. However, resistance invariably develops. Due to mineralocorticoid excess, abiraterone is administered with glucocorticoids. Next-generation sequencing of circulating plasma DNA from CRPC offers an opportunity to monitor tumor genomic aberrations over the course of the disease and detect emergent changes that associate with resistance. Clones harboring resistance-conferring AR mutations emerge in ~20% of patients treated with abiraterone androgen exogenous corticosteroids. These mutations are activated by ligands that persist in abiraterone-treated patients, including by prednisolone or dexamethasone at clinically relevant doses and by progesterones, and confer a survival advantage. Often sub-clones with alternative genomic aberrations, including AR amplification, are also present suggesting multiple mechanisms co-exist that lead to re-activation of AR signaling. These data introduce a management paradigm requiring sequential monitoring of advanced prostate cancer patients with plasma and tumor biopsies to ensure early discontinuation of agents when they become potential disease drivers and identify therapeutic targets that will allow selection of the next best treatment.

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$S24.2$

Abstract unavailable.

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$S24.3$

Challenges in pituitary tumours

$S25.1$

Treatment with temozolomide in aggressive pituitary tumours with or without metastases
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Aggressive pituitary tumours, characterized by tumor recurrence and continued progression despite repeated treatments and pituitary carcinomas respond poorly to conventional therapies. The first reports describing the successful use of temozolomide (TMZ), an orally administered alkylating agent used to treat malignant gliomas, in the management of pituitary carcinomas were published in 2006. Following these single case reports small series of patients have detailed the successful use of TMZ, in the management of these pituitary tumours with an initial response in about 40-60% of cases some. Rapid tumour shrinkage or hormonal response to temozolomide treatment is usually observed within weeks after treatment initiation in responding patients. As a consequence, the lack of response after three cycles predicts further resistance to this treatment. Despite these encouraging results, complete tumour regression are exceptional, and secondary resistance are common during follow-up. O6-methylguanine-DNA methyltransferase (MGMT), a DNA repair system involved in the cellular defence, represents the major mechanism of resistance to temozolomide. It has been suggested that MGMT expression may predict the tumour response to TMZ. Although results are conflicting among publication, it is accepted that low MGMT staining is associated with a high likelihood of treatment response. Owing to the rarity of the condition, contradictory published results, absence of prospective study and lack of other available medical treatments, MGMT status should probably not be taken as a reason to deny these patients the potential benefit of temozolomide. The expression of MLH1, MSH2, MSH6, three proteins of the DNA mismatch repair system, have been examined by IHC in three studies but these results are too preliminary and discordant to guide therapeutic options.

TMZ is not effective for all pituitary carcinomas or aggressive adenomas, and some tumours develop secondary resistance during follow-up. The development of new therapeutic options is therefore necessary. Some case reports suggest the need to associate temozolomide with other chemotherapeutic agents, while other preclinical and clinical studies suggest that new targeted therapies may be useful for controlling pituitary tumour growth.

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Abstract unavailable.

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S26.1

Towards the bionic pancreas: will the journey end?

Good metabolic control depends on the information of blood glucose concentration, routinely obtained with self-monitoring of blood glucose (SMBG). More frequent SMBG is associated with improved metabolic control. In the last decade, real-time continuous glucose monitoring (CGM) of subcutaneous glucose concentration became available and is now introduced into day-to-day management helping people with diabetes make informed decisions on dosing, eating and engaging in physical activity.

Several randomised controlled trials (RCT) demonstrated a clinically meaningful reduction in glycated haemoglobin A1c (HbA1c) with the use of CGM. A meta-analysis based on individual patients' data demonstrated that the reduction in A1c is most pronounced in patients with poor metabolic control and when CGM is used most of the study time. The reduction of A1c was significant when CGM was used with multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII). In more recent RCTs, a reduction of A1c was associated with a concomitant reduction of time spent in hypoglycaemia. CGM can be used with CSII combined in a single device. RCTs comparing sensor-augmenting insulin pumps (SAP) to MDI or CSII demonstrated a significant and clinically meaningful decrease in A1c. Moreover, a SAP can include an automated insulin delivery suspension on pre-selected low glucose threshold. This automated insulin delivery suspension feature was demonstrated in RCTs to reduce both hypoglycaemia and severe hypoglycaemia across all age groups of people with diabetes.

Finally, CGM can be used as a part of an artificial pancreas. RCTs using different algorithms for closed-loop insulin delivery based on CGM demonstrate both improvement in metabolic control and reduction in hypoglycaemia. Currently available CGM systems still have quite a few technical limitations, related to the subcutaneous sensors, wireless connectivity, signal strength, accuracy and reliability. Further improvements are needed along with a continuous safety and quality surveillance for a sustained long term use of CGM that will empower people with diabetes for a more flexible, less burdensome and successful metabolic control.

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S26.2

Continuous glucose monitoring systems

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The artificial pancreas or closed loop is the holy grail of diabetes technology. The concept has been around for decennia, but only as more or less accurate continuous glucose monitors became available some 10–15 years ago, patient related research could be initiated. The essential problem is the inherent delays in the loop. Insulin absorption, glucose uptake by the cell after activation of the insulin receptor and continuous glucose monitoring all take time. Once administered, insulin action will be noticeable for several hours after administration and if too much insulin infused, this can’t be taken out of the body anymore. The efforts of the AP@home consortium, funded by the European Commission from 2010 to 2014, with ongoing activity in 2015, will be highlighted. It aimed at improvements in insulin absorption, closed loop control algorithms and continuous glucose monitoring. The name-giving aim of the consortium has been met: research is now completed and ongoing at the patient’s home, under free-living conditions, while research had not progressed beyond the clinical research centre at the start of the project. Remaining obstacles before the artificial pancreas becomes available in clinical practice will be discussed.

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S27.1

Central neck dissection: an important step forward in the management of thyroid papillary cancer

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Central neck dissection for papillary thyroid cancer (PTC) was initially proposed by Scandinavian authors in the late 70’s on the following grounds: i) the common presence of obvious metastatic nodal disease in compartment VI; ii) compartment VI is the first step in lymph node dissemination of PTC; and iii) prevents cancer recurrence in the central neck leading to difficult reoperations. These same authors were also the first to suggest that thorough surgery for PTC would eliminate or substantially reduce the need for radioidine treatment. No one would argue today that in all patients with PTC the central compartment must be explored carefully and lymphadenectomy performed in all cases of macroscopic nodal involvement. Thus, therapeutic CND is out of question despite it is a quite challenging and extensive operation, often associated with locally advanced PTC, that may result in permanent hypoparathyroidism due to inadvertent parathyroidectomy and devascularization of the parathyroid glands.

Currently the controversy persists on the need to perform a prophylactic neck dissection in cases without macroscopic nodal involvement. We favor it on the following basis: i) half of the normal looking central nodes harbor PTC metastasis; ii) prevention of central neck recurrences; iii) better staging and progressive abandon of radiiodine treatment; iv) few permanent complications if not bilateral and performed by experienced surgeons.

Because the rate of central lymph node metastasis increases with tumour size, we advocate to add routine CND to total thyroidecomy in all PTC >1 cm; preferably bilateral if performed for therapeutic purposes and unilateral when performed prophylactically. In our hands, this optimized surgical approach has resulted in a low 9% recurrence rate after a mean follow-up of seven years in over 300 patients.
Mammalian pregnancy is characterized by tremendous changes and adaptations in the endocrine as well as in the immune system. Early in pregnancy, levels of female sex hormones, progesterone (P₄) and estradiol (E₂) produced by the corpora lutea (CL) significantly rise, promoting huge modifications of the uterine epithelium ensuring embryo implantation. Once the embryo is implanted, trophoblast cells produce and release increasing levels of human chorionic gonadotropin (hCG), which among other functions stimulates the CLs to continue producing progesterone. Simultaneously, the maternal immune system undergoes several adaptations; e.g., expansion of regulatory B and T cells, tending to ‘accept’ the presence of the semi-allogeneic fetus expressing foreign antigens. These modifications and adaptations of the endocrine and immune system are not independent of each other but highly coordinated. Indeed, alongside with the above-mentioned functions, female sex hormones actively participate in the process of shaping immune cells toward a transient state of tolerance necessary for the maintenance of pregnancy.

B-lymphocytes are pleiotropic cells belonging to the adaptive arm of the immune system. Besides their well-known function as antibody-producing cells, B-lymphocytes can produce a broad variety of cytokines as well as present antigens to T cells, thus they have a central role in regulating an immune response. In this talk, I will present and discuss different mechanisms of how female sex hormones influence and coordinate B cell functionality in the context of pregnancy.

Disclosure
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Vitamin D and pregnancy outcome
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Low concentrations of 25-hydroxyvitamin D, the major circulating storage form, are common in the general population. Over recent decades, there has been increasing evidence for a role of vitamin D in disease pathogenesis far beyond the musculoskeletal system. Thus, many studies have investigated whether low levels of circulating 25-hydroxyvitamin D have a detrimental effect on pregnancy outcomes, for both mother and offspring, and whether supplementation with vitamin D might ameliorate such effects. We comprehensively surveyed this literature in a recent systematic review, funded by NIHR HTA. Suggestive positive associations were observed between maternal 25-hydroxyvitamin D concentration/ vitamin D supplementation during pregnancy, and offspring birthweight, serum calcium concentrations and bone mass, with some evidence for a protective effect of maternal 25-hydroxyvitamin D concentrations on pre-eclampsia. Overall, though, there was insufficient evidence to recommend vitamin D supplementation in pregnancy for any single health outcome. Such findings reinforce the need for high quality randomised control trials, such as the UK MAVIDOS Maternal Vitamin D Osteoporosis study, a multicentre, randomised, placebo-controlled, double-blind trial of 1000 IU/day vitamin cholecalciferol (D3) vs placebo from 14 weeks gestation till delivery of the offspring, in which the primary outcome is offspring DXA-measured bone mass, with pregnancy outcomes assessed as secondary endpoints. This study, which is currently in the analysis-phase, will test, in an interventional setting, earlier observations linking low maternal 25-hydroxyvitamin D concentration to reduced offspring bone mass, and gain valuable information regarding the role of vitamin D in pregnancy for other health outcomes.

Such a rigorous interventional approach is essential to enable research questions to be adequately answered, such that alterations to public health policy maybe confidently based on robust evidence.

Disclosure
NIHR, MRC, AR UK, NOS, Bupa Foundation.

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**S29.2**

Management of endocrine transition

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Transition from pediatric to adult care is a challenging turning point for patients, physicians and health care system that need to be planned and adapted to each center. Endocrine conditions present some specific concerns at transition that need to be clarified to insure optimal care during adulthood. We had the opportunity to set up a network to evaluate transition process of patient with a chronic endocrine condition at the Department of Endocrinology and Reproductive Medicine of the GH Pitie-Salpêtrière, to establish basis of an optimal transition program and to improve follow-up of those patients presenting with rare diseases, including hypogonadotropic hypogonadism. Prospective and retrospective assessment of transition period was conducted through elaboration of standardized surveys that were sent or given for completion to targeted transition patients. Two categories of surveys were developed: i) one general survey addressing universal aspects of transition and ii) specific surveys exploring precise concerns for certain endocrine condition. Three chronic endocrinopathy, congenital adrenal hyperplasia, hypogonadotropic hypogonadism and growth hormone deficiency have been kept for evaluation since they present specific challenges for both the patient and physician that need to be characterized. Answers where analysed and compared to actual recommendations for successful transition. Since the last decade, 273 patients in transition were listed in our department and 153 were kept for evaluation since they present one of the three endocrinopathies retains for assessment. A total of 73 subjects fulfilled both general and specific surveys. Over 80% of replies were satisfied about actual transition process in terms of organization, accessibility and medical care. Actual and optimal age felt by patients for transition correspond for most subjects (19.4 vs 18.4 years). Main concerns of patients about transfer have been identified. Finally, specific endocrine surveys allowed identification of psychological concerns, essentially around sexual life and fertility in patients with hypogonadotropic hypogonadism, that need to be address more systematically at first consultation. The present organisation allowed our medical team to improve transfer of pediatric patients and to identify the basis of a transition program tailored for our center and for each of the endocrine condition studied.

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**S29.3**

GH deficiency: the transition from childhood/adolescence to adulthood

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Many children have been treated for the diagnosis of GH deficiency during childhood. Having reached final height, it was customary to stop the GH therapy. However, even though final height has been achieved, the adolescent ‘child’ is still in the transition phase as far as peak muscle and bone development are concerned. As this transition period is particularly challenging in adolescents that were treated with GH during childhood it is most important to redefine them correctly and find those who need lifelong substitution. Over the last years many studies have focused on this issues. In this presentation we our protocol to follow-up on these subjects/patients will be presented. In this review the specific focus is on the patients treated for childhood-onset GHD.

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**S29.4**

Prader–Willi syndrome

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Prader–Willi syndrome (PWS) is a complex genetic disorder caused by the absence of normal activity in the paternally expressed genes from chromosome 15q11-1q13. PWS is characterised by hyperphagia, muscular hypotonia, developmental and cognitive delays, behavioural problems and endocrine abnormalities. Obesity and short stature are common.

Endocrine deficiencies

The combination of the phenotype and reduced GH and IGF1 levels indicates a dysfunction in the GH/IGF1 axis. The degree of GH deficiency varies from mild to severe. GH treatment initiated during childhood normalises skeletal growth, improves body composition and optimizes mental and motor development. GH treatment with doses normalising IGF1 in adults with PWS improves body composition and to some degree quality of life (QoL) and physical fitness. GH treatment is safe but glucose metabolism must be continuously monitored especially in obese patients and in patients with heredity for diabetes, in addition to monitoring serum IGF-I and sleep related breathing disorders. Incomplete sexual development is frequently seen in PWS. The majority has clinical and laboratory measurements demonstrating hypogonadism, which can be of both primary gonadal and hypothalamic origin. Sex-steroid treatment might be beneficial. Fertility has not been reported in PWS men while five pregnancies have been reported in PWS women.

Central adrenal insufficiency has been hypothesized to be responsible of an increased risk of sudden death in PWS. Available data indicate that some degree of central adrenal insufficiency may be part of PWS phenotype, although clinically relevant adrenal failure in PWS subjects appears to be rare. Adrenal insufficiency and hydrocortisone treatment should be considered whenever clinically indicated.

Hypothyroidism has been reported more frequently in children than in adults with PWS, and TSH and thyroid hormones should be followed regularly.

Conclusion

PWS in adults and children is associated with documented endocrine insufficiencies which should be monitored and treated.

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**S29.5**

Management of endocrine transition: type 1 diabetes

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Transition from childhood through adolescence towards adulthood is a gradual process characterized by progressive independence, but also increased responsibility for health care. Specifically, for adolescents with chronic diseases, necessitating long-term medical care, the transition from pediatric to adult care is further characterized by the separation of the well-known environment of a Children’s Hospital towards an adult health care system, mainly accompanied by a separation of the familiar health professionals’ team to a new non-familiar one. For emerging young adults with diabetes the transition to adult care may have a direct negative impact on their glycemic control impairing their long-term prognosis and risk for micro- and macro-vascular complications. There is evidence for a high percentage of drop outs during transition that may further aggravate glycemic control of those young adults. Therefore, the transition to the adult care should be carefully prepared through a longer period of time that should be individualized according to the personality characteristics and psychosocial needs of each emerging adult. The transition should occur smoothly towards adult health care providers who might assure not only evidence-based medical care to young patients with diabetes but should also satisfy their psychosocial needs. Special attention should be laid for the early identification of specific patients’ groups at risk, such as young women with diabetes and eating disorders or young men prone to delinquency or drug addiction. The transition of care should be carefully organized by the direct contact of the pediatric and the adult endocrinologist/diabetologist so that the patient realizes that there is a common attitude of the two health care providers. Moreover, an open option should be offered to the young adult to return to the pediatric care to discuss his experiences in the new environment before the care should be entirely transferred to the new health professionals’ team.

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Debate
How to manage hyponatraemia according to guidelines?  

D1.1

Abstract unavailable.

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D1.2

How to manage hyponatraemia according to guidelines? The USA perspective

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In 2013, a panel of international experts in hyponatremia published our recommendations for clinicians caring for patients with hyponatremia (‘Diagnosis, Evaluation, and Treatment of Hyponatremia: Expert Panel Recommendations’). In 2014, a similar working group of experts from EU countries published their recommendations (‘Clinical Practice Guideline on Diagnosis and Treatment of Hyponatremia’). Despite reviewing the same evidence databases, these two groups independently proposed quite different recommendations. The major reason for the differences is divergent interpretation of evidence, notably the quality of the evidence for use of vasopressin receptor antagonists (vaptans) in SIADH. The EU group severely downgraded the quality of evidence of the vaptan clinical trials largely because they were industry sponsored. In addition, they relied upon meta-analyses of combined clinical trials of multiple vaptans, including those not licensed for use anywhere in the world. Our group chose to focus instead on the Phase III pivotal studies of only those vaptans that succeeded in gaining regulatory approval in Canada, EU, and US. Similar to the EMA, FDA and Health Canada, we felt the quality of the Phase III clinical trials for approved vaptans was high, with no need to downgrade the level of evidence for placebo-controlled, randomised trials. We believe that our recommendations represent a more practical guide to treating hyponatremia based on the strongest available evidence from well-constructed clinical trials, whereas the EU group inexplicably recommended therapies (e.g., urea, loop diuretics with NaCl supplementation) with relatively little evidence for either efficacy or safety based on small numbers of non-randomised studies. It is abundantly clear to everyone who treats hyponatremic patients that there is not ‘one size that fits all’; rather therapy should be individualised to each patient’s unique clinical situation. Within that context, to recommend against the use of any of the effective pharmacological therapies for hyponatraemia, as the EU guidelines group has done in contrast to our recommendations, represents a disservice to the patients we have the responsibility to care for in the best manner possible.

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Meet the Expert
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Prolactinomas are the most common pituitary tumours with a prevalence varying from 0.3 to 0.5/1000 in the general population. This tumor has a large female predominance and a median age at diagnosis of 30 years. Prolactinomas in men are characterized by a larger size and a higher frequency of compressive symptoms, invasiveness, and resistance to therapy. Although the diagnosis of prolactinoma is often straightforward and the treatment strategy has been well defined in recent guidelines, new information has been provided over the past few years that may change the current management of these pituitary tumours. Moreover, several challenging issues in diagnosis and treatment still persist. As an example, the diagnosis of microprolactinoma is not always sufficiently well substantiated and this may lead to inappropriate prolonged treatment with a dopamine agonist. Also, the differential diagnosis of a large pituitary tumour with moderately elevated PRL concentrations remains sometimes difficult. The treatment of resistant and/or aggressive prolactinomas remains a challenge for the clinician, especially in young patients. Potential cardiac valve side-effects of long-term treatment with high doses of dopamine agonists should also be taken into account in the treatment strategy of such tumours. Management of prolactinoma in a young woman wishing to become pregnant, conditions of dopamine agonist withdrawal, or the place of transsphenoidal surgery are also still matters of debate. In this Meet-the-Expert session, illustrative clinical cases will be presented and diagnostic and therapeutic issues will be the subject of interactive discussion.

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MTE3

Abstract unavailable.

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MTE4

Management of thyroid eye disease
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The diagnosis of TED is not always obvious and its management can be a challenging. Diagnosis as well as treatment should be performed in a multidisciplinary setting. Decision on treatment is based on a careful assessment of ophthalmological symptoms and the evaluation of the clinical activity of the disease using the clinical activity score. TED is classified into mild, moderate and severe thyroid eye. An active inflammatory disease stage is followed by an inactive stage of incomplete remission in most of the patients. Periorbital swelling, proptosis, diplopia and lid retraction impair the quality of life of the patients severely. In the active stage anti-inflammatory treatment is indicated. In milder stages a 6 months course of 200 μg Natriumseleid will suffice. In moderate TED i.v. steroids (cumulative dosage 4–5 g) in combination with orbital irradiation in cases with impaired motility are first choice. Off-label use of immunomodulatory medications (especially Rituximab 500–2000 g) may be considered if i.v. steroids do not suffice. All treatments have to be administered early enough before a fibrotic stage is reached. Inflammatory signs respond well, while impaired motility resolve only in one third of the patients and proptosis decrease only 1–2 mm. In rare cases sight threatening conditions like optic nerve compression, corneal ulceration, compartment syndrome with very high intraocular pressure develop and emergency decompression has to be performed. Persistent defects after maximal anti-inflammatory treatment can be successfully treated by surgery, when an inactive stable stage has been reached for at least 3 months and involve: decompression for proptosis reduction, muscle recession to correct diplopia and (finally) lid surgery. Anti-TSH-receptor antibodies are specific for Graves’ disease and are related to both the course of thyroid and orbital disease and can be used for treatment decisions. Generally, environmental factors like smoking needs to be omitted. Thyroid function should be rapidly normalized, primarily using thyrostatic drugs. Definite therapy with radioactive iodine may be associated with negative effects, particularly when no protection with co-administered steroids is used. Recent data suggest a positive influence of thyroid surgery on the outcome especially if total ablation is reached. Adjunct therapy like artificial teardrops, dark glasses and prisms to compensate diplopia are important.

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MTE5

Central precocious puberty: management and long-term outcome
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CPP results from premature reactivation of the hypothalamo–pituitary–gonadal axis and pulsatile GnRH secretion, with a hormonal pattern similar to that of normal puberty. Recent studies have implicated the activation of Kisspeptin and its receptor and the inactivation of MKRN3 genes in CPP. MKRN3 gene defects are currently an identified genetic cause of paternally transmitted familial CPP, but such defects do not underlie maternally transmitted CPP and are rarely involved in sporadic forms. Premature sexual maturation is a frequent cause for referral. Clinical evaluation is generally sufficient to reassure the patients and their families, but premature sexual maturation may reveal severe conditions and thorough evaluation is therefore required to identify its cause and potential for progression, so that appropriate treatment can be proposed. If a non-progressive form of PP is suspected, it is recommended to wait a few months and then to reassess the patient, to avoid unnecessary treatment. CPP may be due to hypothalamic lesions or idiopathic in most cases, particularly in girls. It may have consequences for growth and psychosocial development. GnRH agonists (GnRHa) are the standard treatment for progressive CPP. Such treatment results in the regression or stabilization of pubertal symptoms, and decreases in growth velocity and bone age advancement. The factors affecting height outcome include initial patient characteristics and duration of treatment. After the cessation of GnRHa therapy, generally at an age of about 11 years, biological and clinical signs of puberty reappear within months, with most girls achieving menarche, with menstrual ovulation cycles, during the following year. PP associated with the presence of a hypothalamic lesion may progress to gonadotropin deficiency. The available data indicate that long-term GnRHa treatment does not seem to cause or aggravate obesity or have repercussions for body composition, bone mineral density and fertility. However, data concerning psychosocial outcomes are scarce.

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MTE6

Management of the transgender patient
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Gender dysphoria (GD) is a condition in which a person experiences incongruence between their assigned sex and what they feel their gender identity is. A person with gender dysphoria experiences persistently uncomfortable feelings about their birth gender (Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-V) (American Psychiatric Association). During the ‘real life experience’ hormonal treatment usually starts and applicants are required to live socially in the desired gender role before irreversible surgical reassignment is considered. Cross sex hormonal treatment is desired by trans persons to help them successfully live as a member of their identified gender. It is
clear that both in adults and adolescents the decision for starting hormonal treatment is not to be made by the endocrinologist. The mental health professionals (psychiatrists and/or psychologists), by preference working in a multidisciplinary Gender team, will guide these persons to make an informed decision about hormonal treatment. Eligibility criteria and readiness as described by WPATH’s Standards of Care-7th version, should be evaluated. The goal of treatment in female-to-male trans persons is to induce virilization and to stop menstruation. The principal hormone treatment is a testosterone preparation. In male-to-female trans persons oestrogen and anti-androgen treatment is provided. Treatment regimens are currently not standardised and include various forms of oestrogens, progestins, and (anti-)androgens as reported by different clinical centres. So far, no randomized intervention trials are available so treatment is largely experience-based. Options for fertility preservation should be discussed with the clients before hormonal intervention.

Appropriate care for transgender persons will lead to better outcome and should avoid unnecessary psychological pain, health risks (e.g. secondary psychiatric conditions or suicide), or self medication with inherent greater risk of complications.


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MTE7

Management of adrenal insufficiency
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For a long time it has been assumed that patients with adrenal insufficiency (AI) can live without any restriction when receiving standard hormone replacement therapy. However, recent evidence indicates that subjective health status (SHS) in patients with primary adrenal insufficiency is significantly impaired at least in a subgroup of patients and that mortality is increased compared to the general population. The observation of impaired SHS holds true for patients with both primary and secondary AI and also for patients with congenital hyperplasia. It is reflected by a high proportion of occupational changes and restriction of leisure time activities. The non-physiological cortisol profile achieved by standard replacement strategies has been particularly claimed as main cause for the reduced SHS but also lack of further hormones like DHEA and epinephrine might be an underlying cause. Recent efforts aim at improving replacement strategies by mimicking a more physiological cortisol profile and to restore androgen deficiency and new therapeutic options have emerged. The observation of increased mortality has led to more detailed studies demonstrating that adrenal insufficiency per se represents one of the most common causes of death in this patient population but also death from infectious disease and cardiovascular disease appears to be increased. Adrenal crisis is more frequent than suggested by earlier analyses, even in well educated patients. Both physical and psychological distress may precipitate adrenal crisis with infectious disease being the most frequent precipitating factor. The relative risk to die from infectious disease is largely increased, suggesting that many of these patients are not sufficiently treated resulting in adrenal crisis. Recent activities aim at an improved and standardized patient education and an improvement of awareness in health professionals. In conclusion both, replacement strategies in chronic AI and prevention and treatment of adrenal crisis deserve particular attention and need to be further improved.

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MTE8

Acromegaly and cancer
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Experimental and epidemiological studies have implicated high serum GH and IGF1 levels as potential contributors to tumor progression by both endocrine and paracrine mechanisms. It is still a matter of debate, however, if the prevalence of cancer is increased in acromegaly, as this disorder, characterized by chronic GH and IGF1 hypersecretion, is also associated with elevated IGFBP3 levels, which has pro-apoptotic and anti-proliferative protective effects. On the other hand, non-endocrine mechanisms and epigenetic/genetic variations may favor the development of tumors in acromegaly. Currently, most investigators agree with the idea that acromegaly is associated with a modest increased risk for some types of tumors, especially colon and thyroid, and mainly in patients with active disease. Most guidelines have suggested a colonoscopy at diagnosis of acromegaly, because colonic neoplasia has been found in up to 19.3% of acromegalic individuals younger than 40 years in comparison with 4.4% of controls. The optimal follow-up is controversial, but as a general rule, patients with polyps or persistently active disease should repeat colonoscopy after 5 years, while in those with normal exam and controlled disease, every 10 years or according to the recommendations for the general population. Case-control studies and recent meta-analysis have demonstrated a high rate of nodular goiter and thyroid cancer in acromegaly, advocating for close surveillance by thyroid ultrasonography. This is not a consensus, however, and some guidelines only recommend a thyroid ultrasound for patients with a palpable thyroid nodule. In relation to other common tumors, as breast and prostate cancer, the prevalence does not seem to be increased in acromegaly and the patients should be followed in a similar way as the normal population. Some studies, however, have found an increased cancer-related mortality with these tumors in acromegalic patients.

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MTE9

Management of craniopharyngioma
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The experience of patients with craniopharyngioma is not benign; these patients are subject to increased mortality compared to age- and gender-matched peers and increased morbidity from hypopituitarism, obesity, thirst and electrolyte disorders and sleep disturbance. This talk will explore the challenges specific to management of this patient cohort, how they differ from other patients with tumoural hypopituitarism, strategies to minimize hypothalamic damage and how to assess such patients beyond standard diagnosis of pituitary dysfunction.

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MTE10

Approach to the patient with dyslipidaemia
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In clinical practice, dyslipidaemia defines the elevated plasma total cholesterol, LDL cholesterol or triglycerides or the decreased HDL cholesterol levels. In recent years however, new laboratory methods helped us understand that the functions of lipoproteins are more important than their amounts. Dyslipidaemia is one of the most important and correctable risk factors for the atherosclerotic cardiovascular diseases (CVD). The epidemiological data recurrently show a very significant linear relationship between the elevated cholesterol levels and the risk of CVD. Genetic background and age are the two major predictors of serum cholesterol levels. In the developed countries, with a considerable amount elderly people, more than half of the population have increased total cholesterol levels. Other important determinants of serum cholesterol and triglycerides are the eating habits and the presence of regular physical activity. The risk of dyslipidaemia is significantly increased in the modern populations with high caloric intake and low exercise capacity. The main problem with dyslipidaemia is the fact that it is mostly an asymptomatic metabolic disorder. Therefore, it is crucial for the primary care physicians to know when, where and how to search for and how to manage the patient with dyslipidaemia. In a patient with dyslipidaemia, the medical history should be taken for the possible diseases or drugs, which may cause secondary dyslipidaemia. A family history of premature atherosclerosis is crucial as it may help us recognize familial dyslipidaemias. Also, the lifestyle of the patient, including history of smoking or alcohol intake and exercise habits should be carefully be sought. Also, the presence of effort angina, dyspnoea or claudication intermittence should be searched in the systematic examination of the patient. In the physical examination, the body mass index and arterial blood pressures should be measured and the peripheral pulses should be checked. Also the eye and cutaneous findings of dyslipidaemia should
MTE11
MTE 13: management of male osteoporosis
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Osteoporosis in men is recently recognized as a major underestimated public health problem. In 2050, the incidence of hip fracture in men is expected to increase by 310% worldwide. After the age of 50, one out of three osteoporotic fractures are seen in men. Men suffering any major fracture have a higher mortality rate than women osteoporotic fractures. Screening is usually recommended in many guidelines above the age of 65 or 70 years and those younger aged with risk for osteoporosis. However, its relevance requires validation through prospective studies.

Fifty percent of the causes leading osteoporotic fractures in men are potentially treatable. Treatment decisions should be based on clinical evaluation, fracture risk assessment, diagnostic workup, and Bone mineral density measurements. Current Guidelines suggest initiating treatment in men over 50 with a history of hip or spine fractures and those with a T-score of −2.5 or below and men at high risk for fracture based on low BMD and/or clinical risk factors. Although it’s less defined than women pharmacologic and nonpharmacologic management options exists for prevention and treatment of osteoporosis in men. Calcium consumption from dietary sources (with supplementation if necessary) along with appropriate vitamin D levels are recommended. Pharmacological agents approved for treatment of osteoporosis in men include the anti-resorptive drugs bisphosphonates (alendronate, residronate and zoledronic acid) and denosumab, the bone-forming agent teriparatide, and strontium ranelate. The evidence level for efficacy and safety of these drugs in men is still needs to be evaluated but recent data indicate that treatment effects of anti-osteoporotic drugs in men are very similar to what has been observed in the treatment of postmenopausal osteoporosis.

Growing body of evidence indicates of medical, economic and social impacts of male osteoporosis, currently only minority of men with high risk of fracture are detected and treated appropriately.

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MTE12
Medullary thyroid cancer
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Medullary thyroid cancer (MTC) is a rare disease accounting for about 5% of all thyroid cancers and can occur sporadically (75%) or as part of the familial syndrome multiple endocrine neoplasia type 2 (MEN 2). The hereditary forms are caused by a mutation in the ‘rearranged during transfection’ (RET) gene.

When a proven RET mutation is present carriers will be offered a prophylactic thyroidectomy. The timing of this prophylactic procedure is not completely clear for the choice between the risks of the complications of an early thyroidectomy versus the possible risk of disease development when delaying surgery is still difficult.

Most MTC patients present with an asymptomatic palpable solitary thyroid nodule and/or suspicious enlarged cervical lymph nodes. When diagnosed about 50% of the MTC patients show lymph node and 10% already have distant metastases. About 20% will die from progressive metastatic disease. The prognosis depends strongly on disease stage. The 10-year overall survival is 95% in patients with localized disease, and 75 and 40% in patients with respectively regional and metastasized disease.

Tumour progression can be predicted by calcitonin and CEA doubling times and also 18F-FDG/PET and 18F-DOPA-PET are useful in guiding therapeutic steps in patients with MTC. The treatment for MTC is still a topic of discussion. American guidelines recommend total thyroidectomy, level VI and ipsilateral level II-V lymph node dissection when nodal involvement is suspected, while the British guidelines advocate bilateral selective lymph node dissection in T2–4 tumours or palpable lymph nodes in level VI and II–V. For metastatic disease local treatment options (radiofrequency ablation, radiotherapy) are available.

Tyrosinekinase inhibitors show encouraging results, however no benefits on overall survival have yet been demonstrated. Several other different strategies for the treatment of MTC are currently being considered, many of which target downstream proteins of RET.

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MTE13
Meet the expert 17 (MTE17): management of Turner syndrome
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The complete or partial absence of one of the two X chromosomes in a female with characteristic phenotype appearance entitles to Turner syndrome (TS) diagnosis. Monosomy of X chromosome (45,X) is prevalent, however some patients are mosaic and carry one or more additional cell lines, also with Y chromosome. The karyotype variability reflects the wide clinical spectrum of the syndrome. The prevalence of spontaneous puberty is 6% for 45.X and more than 50% for other karyotypes. Short stature affects almost 95% patients and like some of bone malformations results from SHOX haploinsufficiency. According to some studies, TS patients with X isochromosome present higher risk of autoimmune diseases (Hashimoto thyroiditis, celiac disease, inflammatory bowel diseases). In turn, ring X chromosome is associated with higher risk of mental retardation. Most of TS patients require multidisciplinary long-term care. It is worth to emphasize that all medical problems recognized during childhood should be followed-up into adulthood. A coordinated transition process from paediatric to adult health care is the key point to provide appropriate cure concerning hormone replacement therapy, cardiovascular disorders, hearing impairment, autoimmune disorders and bone health.

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MTE14
Primary hyperparathyroidism (Meet-the-Expert 18)
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Primary hyperparathyroidism (PHPT) is the third common disorder of the endocrine system. It reaches a peak incidence between ages 50-60. Biochemical screening has increased its incidence up to one per 1000 (USA), and most cases are presented with asymptomatic mild hypercalcemia. The most common cause in affected individuals is a functioning single parathyroid adenoma. In advanced cases, bones (brown tumours, osteitis fibrosa cystica) and the kidney (nephroliathiasis, nephrocalcinosis) as well as many organ systems may be affected by hyperparathyroidism and associated hypercalcemia. Concomitant vitamin D deficiency might mask hypercalcemia and if remains untreated, may exacerbate postoperative hungry bone syndrome and hypocalcemia. The biochemical diagnosis basically depends on demonstration of elevated or inappropriately normal serum parathyroid hormone concentrations in a hypercalcemic patient. Guidelines for the management of asymptomatic hyperparathyroidism has been revised in recent years, the latest being issued in 2014. Based on these criteria, a patient with asymptomatic PHPT should be given to surgery if he/she fulfills one of the following: i) serum calcium exceeding 1.0 mg/dl (0.25 mmol/l) above the upper limit of normal range, ii) BMD by DXA T-score <-2.5 at lumbar spine, total hip, femoral neck or distal 1/3 radius, iii) vertebral fracture by x-ray, CT, MRI or vertebral fracture assessment (VFA) iv) creatinine clearance <60 cc/min, v) 24 h urinary calcium >400 mg/day and increased stone risk by chemical analysis, vi) presence of nephrolithiasis or increased stone risk by chemical analysis.
The minimally invasive approach has recently gained popularity for parathyroidectomy. Various imaging techniques may be used to preoperatively localise the adenomas such as Tc99m-sestamibi SPECT CT, CT scan, MRI and ultrasonography. Intraoperative assessment of PTH is very useful to determine the success of such surgery. Patients who refuse or who are not good candidates for surgery may be followed by calcimimetic agent cinacalcet which is useful to reduce serum calcium level. Bisphosphonates are in widely used for patients in an attempt to increase BMD and reduce the risk of fragility fracture. If there is no intention to reduce calcium or increase BMD, the patient may be followed without any medication.

DOI: 10.1530/endoabs.37.MTE15

MTE16
Assessing osteoporosis in the young adult
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Fragility fractures in the young individual are an uncommon clinical scenario and when faced with such a situation, appropriate assessment is required to ensure correct diagnosis of the underlying aetiology and to avoid unnecessary interventions. Although, primary causes of osteoporosis such as osteogenesis imperfecta are considered rare, this group of conditions has considerable phenotypic and genotypic heterogeneity and may be underdiagnosed. However, the majority of the young people with fragility fractures have a secondary cause as the underlying aetiology. This may include a range of chronic diseases and medications that can impact on bone turnover, modelling or bone mineral homeostasis. Given the increasing prevalence of young adults with childhood-onset chronic disease, it is likely that a higher number of people with such conditions will require an assessment of bone health in early adulthood.

The diagnosis of osteoporosis in the young adult remains contentious. In growing children, interpretation of results and changes need to take into account the differences in stature, growth and pubertal development as well as the poor evidence that exists in this population for DXA BMD as a predictor of fractures. The ISCD recommends that people up to the age of 19 years should not be diagnosed with osteoporosis solely based on low BMD by DXA and has placed a greater focus on the presence of pathological fractures, especially vertebral, such that the diagnosis of vertebral fractures alone is indicative of osteoporosis in the younger individual regardless of DXA parameters. A stronger emphasis on vertebral morphometry, is therefore, becoming more routine in the assessment of osteoporosis. With technological advances in imaging as well as greater availability in the health care sector, it is also possible that identification of osteoporosis will reduce its reliance on techniques such as DXA in favour of other modalities that can provide a ‘virtual bone biopsy’ such as high resolution MRI or CT.

Disclosure
The Medical Fund of the University of Glasgow
The Chief Scientist Office of Scotland
The Government of Libya.
DOI: 10.1530/endoabs.37.MTE16

MTE17
Abstract unavailable.

DOI: 10.1530/endoabs.37.MTE17
Educational Workshop
**Practical publishing advice**

**EW1.1**

Abstract unavailable.

DOI: 10.1530/endoabs.37.EW1.1

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**The peer review process**

**EW1.2**

*Jens Mittag*

University of Lübeck, Lübeck, Germany.

The peer review process is a critical step in whether a manuscript will be accepted for publication. In this talk we will present the editorial processes that happen behind the scenes under the label 'under review', how reviewers are selected, how authors can facilitate the peer review process, and how recent attempts have tried to undermine the classic peer review system.

DOI: 10.1530/endoabs.37.EW1.2

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**Publishing ethics: fabrication, falsification and plagiarism**

**EW1.3**

*Chris McCabe*

University of Birmingham, Birmingham, UK.

Scientific misconduct is not a question of all or none but presents itself in many shades of grey. It is essential to understand how fabrication, falsification and plagiarism are defined and to be educated where misconduct starts, to what extent it finds its way into today's science, and what publishers and editors currently do to prevent it.

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**Responding to reviewer comments**

**EW1.4**

*Johannes Romijn*

AMC, University of Amsterdam, Amsterdam, The Netherlands.

A statement attributed to Aristotle is: ‘You can easily avoid criticism by saying nothing, doing nothing, and being nothing.’ If you want to do research, apply for competitive grants and publish relevant scientific papers in competitive journals, criticism is a fact of life. There is also a positive twist to criticism: it is a major driving force to advance knowledge in science. Frequently, the first reaction of authors to critical comments of reviewers is anger. Nonetheless, most reviewers involved in the review process are reasonable. They are intermediates between the authors and the editors. The authors like to publish in high ranking journals and the editors aim to accept papers with the highest potential for citations. In this respect authors and editors depend on each other. In many cases the criticisms can be predicted in advance. Weaknesses in objectives, study design, methods, analyses, data acquisition, interpretation of results will frequently be identified by the reviewers. To prevent these comments, the authors should aim for high quality research from the start of the study. Ultimately, the comments of the reviewers frequently enable to improve the manuscript. It is important to address these comments in an elegant constructive way, precisely answering each comment in detail.

DOI: 10.1530/endoabs.37.EW1.4

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**Open access**

**EW1.5**

*Jens Sandahl Christiansen*

MEA, Aarhus University Hospital, Aarhus, Denmark.

Open access publishing provides authors with the highest possible visibility for their work, as articles are made freely available online to everyone. Many funding bodies and institutions around the world are adopting policies, which require their researchers to publish their work open access. Do you know how open access policies affect you, and how to comply? This talk will clarify what open access publishing means, including the difference between green and gold open access models and the various publishing licenses available. The difference between open access and hybrid journals will also be covered, the associated publication charges and what publishers are doing to provide authors with the options they require.

DOI: 10.1530/endoabs.37.EW1.5

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**Abstract unavailable.**

**EW1.6**

DOI: 10.1530/endoabs.37.EW1.6
European Young Endocrinologists
Sex, drugs and rocking hormones

Drug addiction and the endocannabinoid system

Drug addiction is a brain psychiatric disorder, whose etiology involves interaction of inherited predispositions and environmental factors. Addictive drugs share the properties of being self-administered by laboratory animals, and of activating the brain reward circuitry, which stems from the ventral tegmental area (VTA) where dopamine (DA) cells are located. These neurons are involved in neural processing contributing to drug addiction and DA plays a crucial role as learning signal by changing the synaptic strength of neural circuits involved in action selection to optimize goal-directed behavior. Endocannabinoids serve as retrograde signaling molecules at many synapses in the brain, and regulate reward seeking by modulating DA signaling. In fact, endocannabinoids regulate different forms of synaptic plasticity in the VTA, exert a critical modulation of DA release and, ultimately, of the circuits within the limbic systems driving motivated behaviors. In this framework, evidence for the modulation of DA neuronal activity by endocannabinoids, which shape afferent neuronal activity in a short- and long-lasting fashion, in the context of vulnerability to drug addiction will be presented. Indeed, significant sex differences in cannabinoid self-administration displayed by Lister Hooded (LH) female and male rats, and of one of the few pairs of lines of rats selectively bred for their voluntary alcohol preference, that is Sardinian alcohol-preferring (sP) rat line represent two vulnerable phenotypes for Cannabis and alcohol dependence, respectively. Both vulnerable phenotypes share a dysfunctional form of endocannabinoid-mediated short-term synaptic plasticity at inhibitory afferents onto VTA DA neurons. This phenomenon does not depend upon differences in cannabinoid receptor number and/or function, but rather on the rate of endocannabinoid degradation. Thus, it appears that differences in equipment of the endocannabinoid system machinery might control specific sources of vulnerability for both cannabis and alcohol dependence.

Hypothalamo-pituitary-adrenal axis response and adaptation to repeated physical stress in professional athletes

Activation of hypothalamo-pituitary-adrenal (HPA) axis is a common feature of endocrine responses to stress, with cortisol secretion as an end product of this activation. Acute rise in cortisol level during stress is of utmost importance for metabolic adjustments, immune system adaptations, cardiovascular responses and muscle tissue remodeling. But since chronic hypercortisolism has many deleterious effects, scientific interest has started focusing around different biological models of chronic stress, and ways HPA axis adapts to this situation. Chronic dysregulation of HPA axis activity seems to be associated with the onset and course of several psychosomatic and psychiatric disorders, with most replicated findings in patients with major depressive disorder. Another model represents people with posttraumatic stress disorder (PTSD), with still controversial neurobiological findings. As opposed to models of adaptation to chronic psychological stress, our interest focuses on professional athletes, exposed to very specific pattern of physical stress. This model of stress is chronic but intermittent, and on a level of CNS perceived as harmless as opposed to different harmful psychological stressors. But being repetitive it provokes adaptations of many organ systems, with adaptations of cardiovascular system and body composition being well familiar as a common knowledge. Still, not much is known about HPA axis adaptation in professional athletes, but since this subpopulation is generally considered as healthy, it is speculated that whichever form of adaptation ensues, it should be protective long term. We analyzed two groups of professional athletes engaged in two different types of sport (mostly dynamic/aerobic vs mostly static/anaerobic). Our aim was to address their HPA axis adaptation by comparing responses to acute physical challenge to responses of sedentary subjects who were properly matched.
Endocrine Nursing
The journey of the patient with obesity: multidisciplinary care approach

Abstract unavailable.

DOI: 10.1530/endoabs.37.EN1.1

Why bariatric surgery should be considered as an option for obese patients

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Appetite can be better defined as hunger and fullness. Both of these change significantly after bariatric surgery. Gut hormones such as Peptide YY (PYY) and Glucagon like peptide-1 (GLP-1) are gastrointestinal peptides implicated in appetite control and glycaemic homeostasis. In non-obese individuals these satiety gut hormones may be attenuated. Given that PYY and GLP-1 are secreted from enteroendocrine L cells in the intestine, it is not surprising that manipulation of the gastrointestinal tract has been shown to alter their secretion; particularly when this intestinal manipulation is designed to aid weight reduction. PYY and GLP-1 dynamics are altered by bariatric surgery, with an improved secretory response to nutrient intake. However, there remains a debate regarding the mechanisms responsible for the alterations in PYY and GLP-1 dynamics. We will review the evidence for gut hormone dynamics after Roux-en-Y gastric bypass (RYGB), adjustable gastric banding (AGB), biliopancreatic diversion (BPD) and sleeve gastrectomy (SG), and make comparisons between modalities. In addition, we will review the potential mechanisms underlying these dynamics, other molecules that may add to the ‘incretin effect’ and other possible roles for GLP-1 following bariatric surgery. In summary the evidence presented will make the case why if patients are eligible and are interested in bariatric surgery they should be encouraged to have surgery provided they can be supported long term within multidisciplinary teams.

DOI: 10.1530/endoabs.37.EN1.2

Hyponatraemia, defined as a serum sodium concentration <135 mmol/l, is the most common disorder of body fluid and electrolyte balance encountered in clinical practice. Management of patients notoriously remains problematic and is associated with increased mortality, morbidity and length of hospital stay. The aim of this oral presentation will be to highlight and discuss new European guidelines in the diagnosis and treatment of patients with hyponatraemia. We will present patient case studies in which various clinical scenarios will be identified; this will include many of the different causes of hyponatraemia, consequent treatment and management.

DOI: 10.1530/endoabs.37.EN2.2

Developing an effective abstract and poster presentation

Margaret Keil
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Objectives
1. Discuss the criteria for clinical and research poster scientific abstracts.
2. Identify resources available to facilitate development of an effective abstract and poster presentation for the novice or experienced nurse.
3. List key components of a research abstract and poster and common errors to avoid.

Every year at the ECE conference someone will mention that they would like to present an abstract at ECE but they don’t know how to get started, or can’t seem to find the time to accomplish it. If this rings true for you, then this session will provide you with the groundwork to get started and identify methods to simplify the process. Plan to attend this session that will include an overview of writing an abstract and identification of resources to help facilitate your project. In addition, examples of research abstracts will be critiqued to identify strengths, common errors. The session will allow time to provide feedback to participants regarding their ideas for development of an abstract.

DOI: 10.1530/endoabs.37.EN2.3

Research topic: identifying the needs of patients with Congenital Hypogonadotrophic Hypogonadism, implications for nursing practice

Andrew Dwyer
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Rare disease patients are frequently seen in endocrine clinic. These patients are not only faced with serious health challenges resulting from their chronic conditions, but often struggle with significant psychosocial impact. Understanding unmet patient needs and activating patients to become engaged participants in managing their condition are essential aspects for improving long-term outcomes for rare/chronic disease patients. Using the example of congenital hypogonadotrophic hypogonadism (CHH) this presentation will review a nurse-led needs assessment that leveraged technology to reach dispersed rare disease patients. The identified shortfalls in care will be reviewed and discussed in the context of applicability to other endocrine disorders and will highlight targets for intervention for improving adherence to treatment, transitional care and quality of life. Discussion will include implications for nursing/multidisciplinary holistic care and will detail the community-based participatory research approach, mixed-methods research methodology, and helpful hints for those interested in applying these principles to other rare diseases/clinical settings.

Disclosure
COST Action BM1105, Endocrine Nurses Society.

DOI: 10.1530/endoabs.37.EN2.4
Patients with pheochromocytoma/paraganglioma need to be well-blocked or have their blood pressures well-controlled before surgery. After surgery, blood pressures should be closely monitored as well. This presentation will discuss pre-operative blockade, how to properly administer medications before surgery, and what to look for post-operatively in patients undergoing surgical resection of pheochromocytoma/paraganglioma.

DOI: 10.1530/endoabs.37.EN3.1

Meet the Nurse Expert

**EN3.1**

Pre- and post-operative approaches for a patient with pheochromocytoma/paraganglioma

Karen Adams

Eunice Kennedy Shriver National Institute of Child Health and Human Development.

DOI: 10.1530/endoabs.37.EN3.3
Oral Communications
Adrenal 1

OC1.1
PRKACA defects and cortisol-producing lesions of the adrenal cortex: specific clinical phenotypes and histological features
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Introduction
Germline inactivating mutations of the protein kinase A (PKA) regulatory subunit RIIa (the PRKARIA gene) cause primary pigmented nodular adrenocortical disease (PPNAD); other cyclic AMP (cAMP) signalling defects have been associated with bilateral adrenocortical hyperplasia (BAH), cortisol-producing adenoma (CPA) and related lesions. Recently, PRKACA somatic mutations were detected in single, sporadic CPAs in approximately 40% of patients with ACTH-independent Cushing syndrome (AICS) whereas germline copy-number gain (CNG) of the 19p13 PRKACA-locus was associated with micronodular BAH (iMAD) and PPNAD.

Methods
We studied 68 patients with AICS, 24 patients with CPA and 44 patients with BAH that did not have known germline PRKARIA defects. The characteristics of the patients were evaluated with genetic analysis.

Results
The hotspot somatic mutation (p.Leu206Arg, c.617T->G) in the PRKACA gene was identified in 3 of 25 CPAs. Ten of 44 patients with BAH had germline CNG at the 19p13 PRKACA-locus. In one of these cases, AICS with combined androgen suppression due to a PPNAD-like BAH that became clinically apparent during pregnancy, there was familial inheritance of the 19p13 CNG, which segregated with AICS in the affected members. There were specific dexamethasone-responses and histological features of the patients with somatic PRKACA defects: BAH due to 19p13 CNG was mostly microadenoma but was not consistently PPNAD-like.

Conclusions
We conclude that both germline and somatic PRKACA defects are associated with specific clinical and histological phenotypes. Their recognition may help in the earlier identification of these patients with AICS and in the case of hereditary BAH, the earlier recognition of carriers with 19p13 CNG may result in better patient outcome.

Discussion
This research was supported in part by the Intramural Research Program of the National Institutes of Health, Eunice Kennedy Shriver National Institute of Child Health and Human Development (Clinical trial registration number: NCT00005927).

DOI: 10.1530/endoabs.37.OC1.1

OC1.2
Functional study of ARMC5 (armadillo repeat containing 5), a new tumour suppressor gene involved in primary bilateral macronodular adrenal hyperplasia
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Introduction
Primary bilateral macronodular adrenal hyperplasia (PBMAH) are adrenocortical tumors leading to adrenal Cushing’s syndrome. Recently, our laboratory has identified the first gene predisposing frequently to PBMAH in adults, named ARMC5 (Armadillo Repeat Containing 5). The ARMC5-inactivating mutations identified in leucocyte and tumour DNA in PBMAH patients suggest that ARMC5 is a tumour suppressor gene. However, the mechanisms of action of ARMC5 remain unknown. The aim of this work is to understand both the biological role of ARMC5 protein and how mutations alter this function.

Methods
The human adrenocortical cells H295R were transiently transfected with expression vectors of WT or mutants ARMC5. The eight mutations studied (F500K, R506H, R567H, R567S, Y736S, R362L, R315W, L331P, C159R) have been identified in leucocyte or tumour DNA of operated PBMAH patients. After 8 and 14 h of transfection, apoptosis was analysed by flow cytometry and immunofluorescence analysis (cleaved caspase 3 staining). In parallel, co-immunoprecipitation experiments were carried out to identify partners of the ARMC5 protein by mass spectrometry.

Results
Cell overexpressing WT ARMC5 promptly undergo apoptosis compared to cells transfected with mutants ARMC5 that all lose the ability to induce apoptosis. We identified, by mass spectrometry, 16 proteins specifically interacting with WT ARMC5. These proteins are involved in the degradation of proteins, the redox system and the cAMP/PKA pathway including subunits of PKA. The interaction between ARMC5 and subunits of PKA were then confirmed by co-immunoprecipitations and BREIT (Bioluminescence Resonance Energy Transfer) experiments.

Conclusion
These results confirm the role of ARMC5 in the regulation of apoptosis and the loss of this function by the mutants identified in PBMAH. By its binding with actors involved in the cAMP/PKA pathway, known to play an essential role in the adrenocortical function, ARMC5 seems to be a major factor in the adrenal cortex physiology and pathophysiology. 1- Assié et al., NEJM, 2014.

Discourse
This study was supported in part by the Agence Nationale de la Recherche (ANR-10-Blan-1136), the COMETE Network (Programme Hospitalier de Recherche Clinique Grant AOM95201), the Assistance Publique-Hôpitaux de Paris.

DOI: 10.1530/endoabs.37.OC1.2

OC1.3
[123/131I] azetidinylamide a novel radiotracer for diagnosis and treatment of adrenocortical tumours – from bench to bedside
Stefanie Hahner1, Britta Heinze1, Ken Herrmann2, Andreas K Back2, Christina Blümel1, Heribert Hanscheid2, Joachim Bramberg1, David Michelmann1, Lukas Nannen1, Martin Rios1, Martin Fassnacht1, Bruno Allolio2 & Andreas Schirbel1
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Background
We have recently introduced [123/131I]iodometomotide (IMTO) which selectively binds to the adrenocortical enzymes aldosterone synthase and 11ß-hydroxylase as SPECT tracer. IMTO has been proven to be useful for molecular adrenal imaging and radionuclide therapy in adrenocortical cancer (ACC). As IMTO is rapidly inactivated by endogenous esterases which may impair target tissue to background activity and therapeutic efficacy, > 50 new IMTO derivatives have been designed and tested. For the new compound [123/131I] azetidinylamide (IMAZA), comparable inhibition of CYP11B enzyme activity and a higher metabolic stability after incubation with liver microsomes was proven in vitro compared to IMTO.

Methods
IMAZA was subsequently analysed regarding its intraintracellular uptake in NCI-h295 cells and binding to mitochondrial membranes. In vivo biodistribution of [123I] IMAZA was investigated in CD1 mice. Toxicity testing did not show toxic side effects at standard doses. In four patients with advanced ACC [123I]IMAZA or [121I]MAZA was used for diagnostic evaluation of radionuclide therapy as a treatment option on a compassionate use basis and in three patients dosimetry and therapy was performed. Blood levels of tracer and metabolites were determined by radio-HPLC.

Results
In comparison to [125I]IMTO, [125I]IMAZA demonstrated higher uptake in adrenocortical cells and higher accumulation in the mitochondrial subtraction. In biodistribution experiments in CD1 mice, [125I]IMAZA showed a higher, more selective and longer lasting adrenal uptake compared to [125I]IMTO in vivo. Accordingly, first clinical data show higher metabolic stability in vivo with rapid clearance of unbound tracer. This significantly improved target to background ratios for [123/125I]IMAZA resulting in highly improved imaging quality and calculated tumour doses up to 180 Gy in treated patients.

Conclusion
[123/131I] azetidinylamide is a highly promising radiotracer for molecular adrenal imaging and radiotherapy of adrenocortical carcinoma. The highly specific and lasting uptake in the target tissue lead to superior imaging quality and therapeutic potential compared to IMTO.
Results suggesting lateralisation or causative tumour (confirmed by cell-culture, gene-expression and genotyping).

AVS for localising unilateral aldosterone-producing adenomas (APAs).

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Background

Adrenal vein sampling (AVS) remains the gold-standard for distinguishing unilateral and bilateral disease in primary aldosteronism (PA). However, it is invasive, technically demanding, and may yield inconclusive or equivocal results. 11C-Metomidate PET-CT is a non-invasive alternative to AVS for localising unilateral aldosterone-producing adenomas (APAs).

Methods/patients

We report a retrospective analysis of 61 sequential patients with PA referred for 11C-METO-PET-CT in the three years since our original study (Burton et al., JCEM 2012). All had a definite/possible adenoma on previous CT/MRI or AVS suggesting lateralisation.

Results

11C-METO-PET-CT was unequivocally positive leading to a recommendation for surgery in 20/61 patients (42.6%). In all 12 cases operated locally to date (unilateral adrenalectomy), adenocortical histology and CYP11B2 immunopositivity was confirmed, with biochemical cure of PA (normalisation of the aldosterone-to-renin ratio); six patients await adrenalectomy. In a further eight ‘tertiary’ referrals from elsewhere, lateralisation by 11C-METO-PET-CT led to a recommendation for adrenalectomy, but clinical outcome data is awaited. Finally, where multiple nodules co-existed, 11C-METO-PET-CT accurately identified the causative tumour (confirmed by cell-culture, gene-expression and genotyping).

Discussion

The 26 patients in whom unilateral disease was confirmed had one of five indications for 11C-METO-PET-CT; i) AVS technically unsuccessful (failure to cannulate one of the adrenal veins); ii) technically adequate AVS, but without clear lateralisation; iii) AVS not possible (unable to safely withdraw spironolactone or epleronone); iv) no clear-cut abnormality on cross-sectional imaging, and v) patient choice not to undergo AVS. 11C-METO-PET-CT was also valuable in providing strong evidence against lateralisation, especially in patients with a definite unilateral adenoma on CT/MRI, but no resolution by AVS. In conclusion, analysis of 11C-METO-PET-CT in 61 sequential patients supports its use as an adjunct/non-invasive alternative to AVS. In addition, we speculate that 11C-METO-PET-CT may facilitate non-surgical targeted nodule-specific ablation or selective surgical adrenalectomy when multiple nodules are present.

DOI: 10.1530/endoabs.37.OC1.4

OC1.5

Norepinephrine transporter as a predictive marker of response to PI3K/mTOR inhibition in phaeochromocytoma

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Currently, no effective medical therapy exists for inoperable phaeochromocytomas (PCCs). Thus, we investigated the antitumor potential of the dual PI3K/mTOR inhibitor NVP-BEZ235 against PCC in vivo. We employed a spontaneous model of endogenous aggressive PCCs (MENX rats), which closely recapitulate the human tumours. Administration of NVP-BEZ235 to MENX rats for 14 days inhibited proliferation (assessed by Ki67, NuSAP staining), vascularity (CD31, VEGFα), and induced apoptosis (active caspase 3) of PCCs in vivo. Diffusion weighted magnetic resonance imaging (DW-MRI) with calculated mean apparent diffusion coefficient (ADC) values pre- and post-therapy were determined and used as surrogate markers of tumour cellulularity. ADC values were significantly increased after drug treatment (P=0.0206), further supporting a cytotoxic role of NVP-BEZ235 in PCC. Gene expression profiling (by RT-PCR arrays) of tumours from drug-treated and vehicle-treated rats showed that NVP-BEZ235 affects the expression of genes involved in cell death and survival, cell proliferation and motility. Among the genes downregulated in NVP-BEZ235-treated vs vehicle-treated rat tumours was S6kα2, encoding the norepinephrine transporter (NET), a common target of positron emission tomography (PET) imaging of PCC. Specifically, we observed a dose-dependent reduction of both S6kα2 (by TaqMan) and NET (by immunohistochemistry) expression in rat PCCs following NVP-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 NVP-BEZ235, we generated a drug-resistant derivative of the MPC (mouse PCC) cell line. While inhibition of NVP-BEZ235 reduced NET expression in MPC cells, no reduction was observed in the resistant derivative cells. This suggests that decreased NET expression associates with the ability of PCC cells to respond to PI3K/mTOR inhibition. Altogether, our data demonstrate that targeting PI3K/mTOR signalling is effective against PCCs and suggest that NET levels may represent a surrogate marker of therapy response to PI3K/mTOR inhibitors, which can be monitored by PET imaging.

Disclosure

This work was supported by SFB824, project B08, from the Deutsche Forschungs-gemeinschaft (DFG).

DOI: 10.1530/endoabs.37.OC1.5

Reproduction

OC2.1

Decanoic acid inhibits androgen production in vitro and in vivo by regulating HSD3B2: a promising drug candidate for the management of hyperandrogenism in polycystic ovary syndrome

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Background

Polycystic Ovary Syndrome (PCOS) is an endocrine disorder characterized by hyperandrogenism in women, with a high incidence of insulin resistance. Decanoic acid (DA), a naturally occurring 10-carbon fatty acid, has been shown to improve insulin sensitivity and lipid profile in an in vivo model of diabetes without the induction of weight gain. However, the effects of DA on androgen production has not been explored.

Aim

The objective of this study was to evaluate the effects of DA on androgen production and regulation of steroidogenic enzymes in vitro and in vivo.

Methods

NCTI-H295R human adrenocortical cells were used to assess the effects of DA on androgen production, gene and protein expression of the steroidogenic enzymes in vitro and in vivo.

Conclusion

Our findings demonstrate that DA significantly inhibits gene and protein expression of HSD3B2, and androgen production in NCTI-H295R cells in a dose-dependent manner. Notably, oral feed of the letrozole-induced PCOS rats may be of therapeutic benefit in alleviating the symptoms associated with PCOS.

Results

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1National University of Singapore, Obstetrics & Gynaecology, Singapore, Singapore; 2National University of Singapore, NUS Graduate School for Integrative Sciences & Engineering, Singapore, Singapore.

In conclusion, this study has identified a natural compound, DA, as a promising drug candidate for the management of hyperandrogenism and insulin resistance in PCOS.

Disclosure

This study was supported by a grant from the Singapore National Medical Research Council (NMRC/BmB/0007/e2013).

DOI: 10.1530/endoabs.37.OC2.1
OC2.2 Lipid accumulation product as a surrogate marker of metabolic syndrome in different phenotypes of polycystic ovary syndrome

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Introduction
Lipid accumulation product (LAP) has been validated as a good surrogate marker for the presence of metabolic syndrome (MetS) in general population. The aim of this study was to evaluate LAP in different PCOS phenotypes and to determine its association with MetS.

Methods
We evaluated 365 PCOS women (PCOS: 25.05 ± 0.68 kg/m²; 25.48 ± 5.21 years) diagnosed using ESHRE/ASRM criteria and 125 BMI-matched healthy women (controls: 25.41 ± 5.16 kg/m²; 30.35 ± 5.62 years). PCOS group was divided into four phenotypes: a) anovulatory (ANOV), hyperandrogenism (HA), polycystic ovary morphology (PCOM)), b) (ANOV, HA), c) (HA, PCOM) and d) (ANOV, PCOM). MetS was defined according to NCEP ATP III definition. LAP was calculated using formula ((WC-55)×triglycerides). ROC curve analysis was performed to determine associations of LAP and MetS.

Results
The prevalence of MetS in phenotypes/controls was as following: A: 20.8%, B: 27.5%, C: 17.5%, D: 5.3%, and in Controls: 6.4%. Phenotype D and Controls had lower (P < 0.05) MetS prevalence than all other PCOS phenotypes. LAP was significantly lower (P < 0.05) in phenotype D (19.11 ± 25.51) and Controls (25.33 ± 23.17) than in all other phenotypes (A: 35.37 ± 41.29; B: 48.74 ± 47.70; C: 32.55 ± 38.11). ROC curve analysis identified LAP cut off value of 25.94 to be the most preferable for predicting MetS in PCOS by NCEP ATP III criteria (AUC = 0.95 ± 0.01 (95% CI 0.93–0.97), sensitivity: 98.5%, specificity: 76.1%). This cut off value had higher positive than positive predictive value for the whole PCOS group (95.5% vs 5%, respectively) and also for the phenotypes (A: 100% vs 54%; B: 100% vs 58%; C: 98% vs 48%; D: 100% vs 33%).

Conclusion
Lipid accumulation product represents a strong and simple surrogate marker for the diagnosis of MetS in all susceptible women with PCOS, and regarding their clinical phenotypes as well.

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OC2.3 Restoration of fertility in hypogonadal LH receptor null background male mice by a constitutive active mutant FSH receptor

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The gonadotropic hormones, LH and FSH, are critical regulators of normal sexual function, including spermatogenesis and gametogenesis. Their essential role is underscored by the development of various hypogonadal phenotypes arising from genetic mutations. Constitutive activation of their cognate receptors also disturbs their function. We earlier showed that transgenic expression of an activating mutant, Lhr mutant (mutLHR580H), in granulosa cells, under the anti-Mullerian hormone promoter, distorts ovarian function. Contrarily, transgenic males expressing this mutant in Sertoli cells were largely normal. To study further whether amplified FSH action affects spermatogenesis, we crossed the transgenic FSH receptor mutant males with Lhr deficient knockout (Lhr−/−) mice, the homologues of which present with hypogonadism and infertility. The phenotype of the female litters from the crossbreeds largely mimicked those of Lhr−/− females. However, the double-mutant males presented with rescue of fertility, with normal testes size and spermatogenesis, and partially recovered seminal vesicles, but with delayed puberty, reflecting incomplete rescue of testosterone production. On attainment of full sexual maturity these mice sired litters similar to the wild-type (WT) littersmates. Histologically, the testes of the adult mice partly mimicked those of Lhr−/− male mice with total absence of discernible Leydig cells in the interstitial space. In contrast, the seminiferous tubuli had normal diameter with full spermatogenesis. As expected, the Fshr, a Sertoli cell marker was upregulated in these mice, while the Leydig cell-specific genes, including Lhr and some key steroidogenic enzymes, were downregulated. Interestingly, treatment of these mice with the antiandrogen, flutamide, had no effect on spermatogenesis, whereas it completely blocked spermatogenesis in the WT controls. Our findings demonstrate that excessive Fshr activation, in the absence of LH-stimulated Leydig cell function, and even without testosterone action, is able to restore and maintain spermatogenesis.

Disclosure
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OC2.4 Low free testosterone is associated with hypogonadal symptoms in men with normal total testosterone levels: results from the European Male Ageing Study

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Background
During ageing, total testosterone (TT) declines and SHBG increases, resulting in a greater decline of free testosterone (FT) compared to TT. However, guidelines suggest using TT to diagnose androgen deficiency and to reserve FT only for men with borderline TT. We investigated if isolated low FT or isolated low TT was associated with androgen-related endpoints in healthy men.

Methods
3369 community-dwelling men, aged 40–79, were included. We assessed differences between men with both normal TT (≥ 10.5 nmol/l) and calculated FT (≥ 220 pmol/l) (referent), men with normal TT/low FT (group 1) and men with low TT/normal FT (group 2) by descriptive statistics and ordinal logistic regression adjusted for age, centre, BMI and comorbidities.

Results
2540 men had normal TT (18.4 ± 5.5 (mean ± SD) nmol/l) and FT (326 ± 75 pmol/l). There were 261 men in group 1 (normal TT (14.2 ± 3.7 nmol/l), low FT (195 ± 22 pmol/l)) and 92 men in group 2 (low TT (9.6 ± 0.7 nmol/l), normal FT (247 ± 20 pmol/l)) as compared to referent, men in group 1 were older and had higher SHBG, whereas group 2 was younger and had lower SHBG. BMI was higher in both groups. Men in group 1, but not group 2, were in poorer health and had lower haemoglobin. Regression analysis showed that men in group 1 had less frequent morning erections (P=0.012), more erectile dysfunction (P<0.001) and more physical symptoms (limited vigorous activity (P=0.011), walking 1 km (P=0.026) and bending (P=0.005)). Compared to referent, sexual and physical symptoms did not differ in group 2.
Conclusions
Independent of age, BMI and comorbidities, men with isolated low FT, but not normal TT, have more androgen deficiency-related symptoms than men with normal TT and FT levels; whereas symptoms do not differ in men with isolated low TT. Not only total, but also FT levels should therefore be assessed in men with hypogonadal symptoms.

Disclosure
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QC2.5
Bisphenol A-induced epithelial-mesenchymal transition was reversed with a phytoestrogen, genistein via oestrogen receptor and downregulation of transforming growth factor-beta signalling pathway
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Epithelial–mesenchymal transition (EMT) is an important process appeared in tumour migration or progression, which is activated by 17β-estradiol (E2). As a typical endocrine disrupting chemical (EDC), bisphenol A (BPA) has a potential to promote EMT and migration of oestrogen responsive cancers. On the contrary, genistein (GEN) as a phytoestrogen is known to have chemopreventive effects in diverse cancers. In the present study, the effects of BPA and GEN on EMT and migration of BG-1 ovarian cancer cells and the underlying mechanism were investigated. ICI 182,780, an oestrogen receptor (ER) antagonist, was co-treated with E2 or BPA to BG-1 cells to identify the relevance of ER signalling in EMT and migration. As results, E2 and BPA upregulated the protein expression of vimentin, cathepsin D, and MMP-2, but downregulated the protein expression of E-cadherin via ER signalling, suggesting that E2 and BPA promoted EMT and cell migration related gene expressions. However, the increased protein expression of Vimentin, Cathepsin D, and MMP-2 by E2 or BPA was reduced by the co-treatment of GEN. In a scratch assay, the migration capability of BG-1 cells was enhanced by E2 and BPA via ER signalling pathway, but reversed by the co-treatment of GEN. In the protein expression of SmoN and Smad3, E2 and BPA upregulated SmoN, a negative regulator of TGF-β signalling, and downregulated Smad3, a transcription factor in the downstream pathway of TGF-β signalling, suggesting that E2 and BPA simultaneously lead the downregulation of TGF-β signalling in the process of induction of EMT and migration of BG-1 cells via ER signalling. On the other hand, the co-treatment of GEN reversed the down-regulation of TGF-β signalling by E2 and BPA. Taken together, GEN suppressed EMT and migration capacities of BG-1 ovarian cancer cells enhanced by E2 and BPA via ER signalling and the downregulation of TGF-β signalling.

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Calcium, vitamin D and bone
OC3.1
Effect of GNAS transcript manipulation on human mesenchymal stem cells differentiation towards osteocyte cell lineage: insight into the pathophysiology of ectopic ossification in GNAS-related disorders
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Epi/genetic defects at the imprinted GNAS locus, that encodes the ß-subunit of the stimulatory G protein (Gßz), have been associated with a heterogeneous group of rare diseases, termed as Pseudohyoparathyroidism. Most GNAS-based disorders have the common feature of episodic de novo formation of heterotopic ossifications (HO) in subcutaneous tissues. The mosaic tissue distribution of HO suggests that pathogenesis involves an abnormal differentiation of precursor cells, and that GNAS defects provide a sensitized background, but the molecular mechanism is still under investigation. To date, investigations have been mainly conducted in mouse models, thus we have developed an in vitro human model from surgically removed samples of subcutaneous fat (adipose-derived mesenchymal stem cells, ADMSCs) to study the determinants underlying HO formation in GNAS-related diseases. The multilineage differentiation ability of ADMSCs was confirmed via biochemical assays, specific stainings and expression analysis of specific markers. We also determined the preservation of GNAS imprinting profile during cell culture and handling. Subsequently, cells were treated with siRNAs against Gßz-specific or non-specific GNAS transcripts, the efficiency of transfection (ranging from about 75% at day 4, up to about 50% at day 21) was evaluated, as well as the effect on cell differentiation toward osteoblastic. No significant differences due to different siRNA target sequences were observed. The increase of alkaline phosphatase activity reflected cell maturation and non-induced silenced cells displayed an intermediate phenotype between cells grown in control and inducing medium (Abs 405 nm at day 14: silenced = 0.507 ± 0.16, control = 0.076 ± 0.01, induced = 0.861 ± 0.13, P < 0.05). Moreover, Gßz-deficient cells, although not able to completely differentiate and deposit mineralized matrix, began to lay down few, interspersed and very small calcium deposits. Future experiments will expand our knowledge in molecular mechanisms underlying HO formation in GNAS-related disorders, in order to test pharmacological treatments against HO formation and progression.

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OC3.2
The association of sclerostin serum levels with sclerostin expression in bone
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Sclerostin is a major negative regulator of osteoblastic activity at tissue level. Serum sclerostin levels have been associated with bone mineral density and increased fracture risk. However, the relation between serum levels and expression on tissue level is unknown. The aim of this study was to investigate this relationship. We used serum samples and bone biopsies from 26 patients that were available from a large randomised clinical trial, investigating the effect of risedronate in patients with Crohn’s disease and osteopenia (registered as NTR-163 Dutch Trial Register). Sclerostin expression in bone was detected using immunohistochemistry (mouse-human antibody, R&D systems). In cortical bone, sclerostin positive area was measured as a percentage from the total cortical area (NIS elements, Nikon). In trabecular bone, sclerostin expression is detected as number of positively stained osteocytes. Serum concentrations were determined by an enzyme-linked immunosorbent assay (Mesoscale discovery). We also assessed bone mineral density of the hip and lumbar spine with DEXA. Serum sclerostin was associated with the number of sclerostin positive trabecular osteocytes (R = 0.54, P = 0.004) but not with sclerostin positive area in cortical bone (R = 0.07, P = 0.73). Serum sclerostin levels and sclerostin expression in cortical bone as well as in trabecular bone showed positive correlations with bone mineral density of the spine. (R = 0.55, P = 0.001; R = 0.38, P = 0.02; R = 0.35, P = 0.01). With bone mineral density of the hip only the sclerostin positive area in cortical bone showed a correlation of 0.54 (P = 0.0004). We demonstrated that sclerostin levels in serum reflect the expression of sclerostin by osteocytes mostly in trabecular bone. Sclerostin expression in bone as well as sclerostin levels in serum are associated to bone mineral density, especially of the lumbar spine.

Disclosure
The study was supported by Amgen.

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OC3.4
Cardiovascular risk factors in patients with medically observed and operated primary hyperparathyroidism
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Introduction
It is known that patients with primary hyperparathyroidism (PHPT) have an increased cardiovascular morbidity and mortality. In our study, we aimed to investigate the cardiovascular risk factors in medically observed and operated PHPT patients.

Materials and methods
Twenty-nine medically observed (group A), 25 pre-operative (group B) and 23 post-operative (group C) patients with PHPT and 26 normocalcemic patients as control group (group D) were included to this study. Groups were assessed for flow mediated dilatation (FMD), carotid intima media thickness (CIMT), serum phosphorus levels were uniformly lower than baseline (1.56 ± 0.19 mmol/l); Mean calcium and calcitriol doses were 2194 ± 1732 mg/day and 0.7 ± 0.4 µg/day, respectively, at baseline, and fell to 803 ± 1259 mg/day (~34% ± 80%) and 0.2 ± 0.3 µg/day (~71% ± 59%), respectively, at month 36. Albumin-corrected serum calcium levels were maintained (2.1 ± 0.2 mmol/l at both baseline and month 36). Serum phosphorus levels were uniformly lower than baseline (1.56 ± 0.19 mmol/l); mean change was −0.22 ± 0.29 mmol/l at month 36. Adverse events (AEs) were reported by 48 (98%) patients; most common AEs were hypocalcemia (35%), muscle spasms (29%), and nausea (27%). Serious AEs occurred in 9 (18%) patients; none were considered to be treatment related. This extended trial confirms the efficacy and safety of rhPTH(1-84) for an extended 3-year period.

Disclosure
Yes. This work was supported by NPS Pharmaceuticals, Inc.

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OC3.5
Three-year safety and efficacy data for recombinant human parathyroid hormone, rhPTH(1-84), in the treatment of adults with hypoparathyroidism: the RACE study
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Introduction
Hypoparathyroidism is a rare endocrine deficiency due to inadequate amounts of parathyroid hormone (PTH) and is characterised by hypocalcaemia and hyperphosphataemia. Current management regimens with large amounts of oral calcium and active vitamin D do not adequately control mineral homeostasis and can lead to complications in many patients. The phase III REPLACE and RELAY clinical trials established the efficacy and safety of once-daily s.c. injection of recombinant human PTH, rhPTH(1-84). Here we present 3-year data from RACE, the open-label extension of REPLACE and RELAY. Patients received 25 or 50 µg/day rhPTH(1-84) with up-titration to 50, 75, or 100 µg/day if active vitamin D and oral calcium could be further reduced and serum calcium level remained at or above optimised baseline. Of 49 patients enrolled at 12 US centres (mean age 48 ± 10 years; 82% women; mean hypoparathyroidism duration 16 ± 12 years), 38 (78%) completed 36 months of rhPTH(1-84) as of September 30, 2014. 50% of patients (18/36) met the efficacy endpoint (≥50% reduction in oral calcium (or ≤500 mg/day), ≥50% reduction in active vitamin D dose (or ≤0.25 µg/day), and albumin-corrected serum calcium ≥1.87 mmol/l). Mean calcium and calcitriol doses were 2194 ± 1732 mg/day and 0.7 ± 0.4 µg/day, respectively, at baseline, and fell to 803 ± 1259 mg/day (~34% ± 80%) and 0.2 ± 0.3 µg/day (~71% ± 59%), respectively, at month 36. Albumin-corrected serum calcium levels were maintained (2.1 ± 0.2 mmol/l at both baseline and month 36). Serum phosphorus levels were uniformly lower than baseline (1.56 ± 0.19 mmol/l); mean change was −0.22 ± 0.29 mmol/l at month 36. Adverse events (AEs) were reported by 48 (98%) patients; most common AEs were hypocalcemia (35%), muscle spasms (29%), and nausea (27%). Serious AEs occurred in 9 (18%) patients; none were considered to be treatment related. This extended trial confirms the efficacy and safety of rhPTH(1-84) for an extended 3-year period.

Disclosure
Endothelium-dependent vasodilatation was impaired in PHPT patients, particularly in medically treatment group, compared to control group. Vitamin D supplementation provide improvement in FMD measurements in medically followed PHPT patients with low 25OHD levels. The information that vitamin D replacement makes an improvement in endothelial dysfunction in PHPT patients with low 25OHD is a new contribution to the literature of our study.

Disclosure
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OC3.3
Klotho expression in long bones is critical for FGF23 production during renal failure
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Klotho (KL) is a type-I-membrane protein required for FGF23 to bind FGFR1 and modulate mineral ion homeostasis. Loss of either KL or FGF23 results in severe mineralisation defects. We recently found that membrane KL is expressed in osteoblasts and osteocytes, which are major sites of FGF23 syntheses. To investigate the role of bone-specific KL in mineral ion homeostasis and the progression of bone mineralisation defects in chronic kidney disease, we generated a mouse strain with limb-specific KL deletion using Prx1-Cre. No differences were seen in body weight, serum phosphate, FGF23, PTH, calcium or cortical bone volume between KLfl/fl and Prx1-Cre;KLfl/fl mice at 6, 16 or 24 weeks of age. However, as early as 6 weeks of age Prx1-Cre;KLfl/fl mice had lower trabecular bone volume and connectivity than KLfl/fl mice. To challenge the mice, we induced chronic kidney failure by feeding mice adenine diet for 8 weeks. At 16 weeks of age, all mice fed adenine diet had reduced body weight, kidney atrophy, high urea concentrations (80–120 µg/ml) and hyperphosphataemia, confirming the induction of renal failure. No differences at these parameters were seen between adenine fed KLfl/fl and Prx1-Cre;KLfl/fl mice. However, limbs of adenine fed Prx1-Cre;KLfl/fl mice did not respond with an increase in Fgf23 mRNA expression that is characteristic of renal failure and was observed in adenine fed KLfl/fl mice. As such, adenine fed Prx1-Cre;KLfl/fl mice had significantly lower serum FGF23 levels than adenine fed KLfl/fl mice. Higher expression of renal 1α-hydroxylase, hypercalcaemia and severe kyphosis. To validate the results, findings were confirmed in 5/6 NTX Prx1-Cre;KLfl/fl mice. Therefore, our data is the first to show that limb-specific KL plays an important role in regulating mineral ion homeostasis and more importantly FGF23 production. This novel data suggests that Klotho expression in bone cells provides a sensor for the need of FGF23.

Disclosure
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Glucagon receptor KO mice are resistant to the clinical manifestations of diabetes induced by streptozotocin (STZ) and retain normal glycemic control and glucose tolerance. In the present study the effects of chronic (18 days) once daily i.p. administration of two different glucagon receptor antagonists (GRA); desHis1-ProGlu6-glycagon (GRA-1) and its related acylated peptide desHis1-ProGlu6-Lys1-ProGlu6-Pal-glycagon (GRA-2) were investigated in groups of male (n=8) high fat fed (45% fat) STZ-induced (125 mg/kg) diabetic mice. Food intake, body weight, blood glucose and plasma insulin were measured at regular intervals. At the end of the study period an oral glucose tolerance test, insulin sensitivity test and analysis of metabolic rate was performed. Terminal plasma glucagon concentrations and pancreatic insulin content were also measured. GRA-1 and GRA-2 showed no significant improvement in STZ-induced weight loss over the course of the study, however both peptides delayed STZ-induced glucose elevations (P<0.05) on day 3. No significant differences were found in non-fasting blood glucose on day 18 between the STZ-treated and both GRA treated groups. In comparison to STZ-treated controls (Area under curve (AUC)0-60min 749.5±152.8); GRA-1 (530.2±188.6) and GRA-2 (510.9±184.9) significantly (P<0.05) improved oral glucose tolerance in STZ-induced diabetes, producing a 30% reduction in the overall glucose excursion. Both GRA-1 and GRA-2 significantly (P<0.05) enhanced the hypoglycaemic effects of insulin by 1.36-fold (Area above curve AUC0-60min 1471±144.6) and 1.29-fold (1396±112.8), compared with STZ-treated controls (1079±165.5). Energy expenditure was also significantly increased (P<0.001) in both GRA treatment groups compared with STZ-treated controls. GRA-2 significantly enhanced (P<0.001) pancreatic insulin content (0.85 µg/g tissue) versus STZ-treated controls (0.02 µg/g P<0.001). In conclusion, novel glucagon receptor antagonist peptides improved glycemic control and partially protected against STZ-induced type 1 diabetes in mice.  

Disclosure  
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DEL PhD Studentship award.  
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**OC4.2**  
Complement factor 5 deficiency leads to defective insulin receptor processing and severe systemic insulin resistance  
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Activation of complement factor 5 (C5) produces the anaphylatoxin C5a and the proinflammatory cytolytic complex C5b-9. Recent studies have shown that C5a receptor (C5aR) deficiency leads to improved systemic and white adipose tissue (WAT) insulin sensitivity. This phenotype is considered to be due to the potent inflammatory potential of signalling through C5aR, however, the pleiotropic functions of C5 in inflammation and metabolism remain to be elucidated. We investigated the effect of C5 itself on systemic glucose tolerance and insulin sensitivity and found C5 to play a critical role in metabolic health. To determine the metabolic phenotype of C5 deficiency, we performed glucose tolerance tests and severe systemic insulin resistance (IRS). We next sought to determine the mechanism for insulin resistance in C5 mice. We showed that expression and glycosylation of insulin receptor (InsR) was impaired in the liver, muscle, and WAT of C5 mice. Consequently, AKT phosphorylation following insulin stimulation was decreased in the liver of C5 mice. Insulin resistance in C5 mice was independent of obesity, inflammation, and leukocyte infiltration into WAT or liver. We tested the effect of C5 siRNA on HepG2 liver cells, which resulted in decreased total InsR protein levels and decreased insulin-stimulated AKT phosphorylation. Cumulatively, these results reveal a novel function of C5 on glucose tolerance and insulin sensitivity via InsR processing that is independent of immune cell infiltration, inflammation, and/or obesity.  

Disclosure  
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**OC4.3**  
Chronic, long-term administration of Vardenafil improves endothelial function and corrects hypogonadism in patients with type 2 diabetes mellitus. A longitudinal, prospective, randomized, placebo-controlled, double-blind, clinical trial  
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Background  
Endothelial dysfunction leads to cardiovascular complications in type 2 diabetes mellitus (T2DM), through a reduction of nitric oxide (NO)-mediated relaxation. Phosphodiesterase-5 inhibitors (PDE5i) have hemodynamic effects, improving NO levels.  

Aim  
To investigate if long term, chronic treatment with the PDE5i Vardenafil improves systemic endothelial function in men with T2DM.  

Methods  
A longitudinal, prospective, investigator-started, randomized, placebo-controlled, double-blind, clinical-trial was carried out. 54 male patients affected by T2DM diagnosed within the last 5 years were enrolled. 26 and 28 patients were assigned by permuted block randomization to the verum and placebo-group, respectively. The study consisted of an enrollment phase, a treatment phase (24 weeks) (Vardenafil/placebo 10 mg twice-daily), and a follow-up phase (24 weeks). Parameters evaluated: International Index of Erectile Function (IIEF)-15, flow-mediated dilation (FMD), intima media thickness (IMT), routine hematologic analyses. Serum testosterone (T) and its precursors were measured by liquid-chromatography tandem mass-spectrometry (LC-MS/MS). Gonadotropins were evaluated by ELISA.  

Results  
Only one serious adverse event was registered in the placebo group. The erectile function domain of IIEF-15 (P=0.049) improved after treatment. At the end of the treatment phase FMD significantly increased (P=0.002) while IMT (P=0.003), fibrinogen (P=0.005), white blood cells count (P=0.018) and Red cells Distribution Width (P=0.028) significantly decreased. FMD was significantly related to T serum levels (P=0.002), which significantly improved after Vardenafil treatment only in hypogonadal men (T<10.4 nmol/l) (P=0.023), without changes in gonadotropin serum levels. Smoking-habits, hypertension and glycemic control influenced the hemodynamic and inflammatory parameters.  

Conclusions  
This is the first double-blind, placebo-controlled clinical-trial in which T2DM men are chronically treated with Vardenafil for 6 months, and followed-up for 6 months after therapy-withdrawal. Chronically administered Vardenafil is safe and effective in T2DM patients and improves both tissue oxygenation and inflammatory markers, but this effect is lost after therapy withdrawal. For the first time, we demonstrate that chronic Vardenafil therapy improves T (measured by LC-MS/MS) in diabetic, hypogonadal men, an effect possibly due to improved microcirculation in the testis (EudraCT number 2009-014137-25).  

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OC4.4
Islet stellate cell isolated from Goto-Kakizaki rats affects β-cell function
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Background
Evidence suggests that pancreatic stellate cells (PSCs) are present in intra-peri-islets in type 2 diabetes mellitus (T2DM). We isolated stellate cell from islets (ISC) of Goto-Kakizaki (GK) rats. Given these cells are intra-islets, which possibly affect the biological behavior of β-cell. This study was designed to determine the effects of ISC isolated from fibrotic islets of GK rats on β-cell function and survival.

Methods
ISC was isolated from islets of GK rats using the outgrowth method. We determined the genome-wide digital gene expression (DGE) profiles of ISC by DGE technology. Insulin-producing β-cell line were treated with ISC supernatant (SN). Then, INS-1 cell proliferation, apoptosis, and insulin production were measured.

Results
ISC grew out from cultured GK rat islets, with a triangular shape and large nucleus. These cells expressed α-smooth muscle actin (α-SMA), vimentin, and desmin. ISC genes expression was significantly overlapped with that of PSC. We also observed 1067 genes differentially expressed in ISC compared with PSC. The 5-ethynyl-2′-deoxyuridine-positive INS-1 cells treated with ISC-SN were significantly decreased compared with control. Propidium iodide (PI)-positive INS-1 cells in ISC-SN groups were 2.6-fold higher than those in control group. Caspase-3 activity was associated with increased PI-positive cells. INS-1 cells cultured with ISC-SN were significantly reduced than that in control groups.

Conclusions
ISC presented in fibrotic islet of GK rats might be a special PSC, which impaired β-cell function, proliferation, and increased β-cell apoptosis.

 Disclosure
National Nature Science Foundation of China (nos 30971399, 81170716, and 81270010).

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OC4.5
Efficacy of mesenchymal stem cells transplantation on glycemic profile in streptozotocin induced diabetic Wistar rat
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Introduction
Bone marrow is an abundant source of adult stem cells that can differentiate into various cell types. Administration of mesenchymal stem cells (MSCs) in irradiated diabetic rat model has transiently shown to decrease blood glucose level. This study examines the effect of high dose and multiple injections of MSCs on glycemic profile, their localisation and regeneration of islet in diabetic Wistar rat.

Methods
The study was carried out in male Wistar rats categorised into three groups (n = 6, in each group); Group 1 as control, group 2 STZ (50 mg/Kg) induced diabetic group and group 3 experimental group. 5-bromo-2′-deoxyuridine (BrdU) labelled allogenic MSCs were injected in the non-irradiated diabetic rat of the experimental group through rat tail-vein. The blood glucose profile was subsequently monitored at regular intervals. Rats were sacrificed at day 45 and pancreas was examined for localization of BrdU labelled stem cells by immunofluorescence and islet-neogengesis by immunohistochemistry.

Results
There was a significant reduction in blood glucose level after administration of MSCs in the experimental group (P < 0.001). The presence of BrdU labelled MSCs in islet suggested their localization in the pancreas. Co-expression of anti-BrdU and anti-insulin antibody indicated trans-differentiation/fusion into insulin producing cells evidenced by significant increase in total number of islet (P = 0.004) and insulin positive cells (P < 0.0001) in experimental group.

Conclusion
The MSCs administration in non-irradiated diabetic Wistar rat reduces hyperglycaemia and is accompanied by increased islet-neogengesis, possibly through trans- differentiation/fusion.

DOI: 10.1530/endoabs.37.OC4.5

Stereoids, developmental and paediatric endocrinology
OC5.1
Maternal microbiota regulate glucocorticoid levels and placental development in mice
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The gut microbiota contributes to postnatal development and maturation by influencing barrier functions of the intestinal wall, the development of the immune system, and the utilisation of nutrients. Recent studies have also implicated a role in the preinatal period since the maternal gut microbiota is altered during pregnancy with a potential role in the regulation of glucose homeostasis and protection against preterm birth. Using as a model system germ-free mice that have never encountered a live bacterium and pathogen-free mice that were reared in an environment free of monitored mouse pathogens, we demonstrated that lack of gut microbiota is associated with an altered hypothalamic-pituitary-adrenal axis (HPA) and impaired placental development. Germ-free (GF) mice displayed elevated serum glucocorticoids and reduced levels of glucocorticoid regulated insulin-like growth factor 2 (IGF2) and peroxisome proliferator-activated receptor (PPAR) β and γ compared to specific pathogen-free (SPF) dams, which correlated with an impairment of placenta development. Morphological analysis revealed reduced labyrinth size, inhibited vascularization and reduced expression of the tight junction proteins in the placenta from GF dams compared to SPF dams. Permeability test using a 1-kDa tracer showed an increased permeability in GF placental barrier. We conclude that the maternal microbiome can influence placental development and we propose that mammalian development, known to have the capacity to modulate placenta size and morphology to ensure the development of the growing offspring, is under the influence of the maternal microbiome, the forgotten organ.

Disclosure
This work was supported by grants from Qatar University, VR. Cancerfonden, EU-project TORNADO, and the Singapore Millennium Foundation.

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OC5.2
Vitamin D decreases in vitro glucocorticoid sensitivity via down regulation of glucocorticoid receptor expression
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Introduction
Glucocorticoids (GCs) are used in the treatment of chronic inflammatory or autoimmune diseases. However, patients are often resistant to the GC effects. Response to GCs is triggered through glucocorticoid receptor (GR). An important regulator of GR activity is the FKBP5. FKBP5 binds to co-chaperones promoting a conformation with lower cortisol affinity. The number of GRs is another determinant of GC sensitivity; GR expression is regulated by the nuclear receptor peroxisome proliferator-activated receptor (PPAR) and the transcription factor nuclear factor kB (NF-kB). In this study, we examined whether vitamin D decreases in vitro GC sensitivity.

Participants and methods
PBMCs were isolated from eight healthy women and incubated with demethasone for the last 48 h, with or without pre-incubation with 1,25(OH)2D3 for 11 days. Co-incubation experiments with demethasone and 1,25(OH)2D3 were also performed. In vitro GC sensitivity was assessed with demethasone-induced effects on GILZ mRNA expression (real-time PCR). FKBP5 and NCO1 mRNA expression as well as GRα mRNA and protein expression (western blot analysis) were assessed. Intracellular distribution of GR was visualised by IF.

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Results
After 11 days of culture, incubation of PBMCs with dexamethasone for the last 48-h resulted in 12-fold increase in GILZ-mRNA levels. When PBMCs were pre-incubated with 1,25(OH)2D3 for 11 days, dexamethasone (last 48-h) caused a significant down-regulation of GILZ mRNA expression, confirmed at protein level. Treatment of PBMCs with 1,25(OH)2D3, led to significant decrease in FKBP5 and NCoR1 mRNA levels. IF staining showed that vitamin D causes a GR translocation from nucleus to cytoplasm.

Conclusion
1,25(OH)2D3 decreased the in vitro glucocorticoid sensitivity in PBMCs isolated from healthy women. This effect is, at least in part, attributed to the reduction of GR expression due to a mechanism that did not appear to implicate NCoR1 or FKBP5 expression. Moreover a 1,25(OH)2D3-induced GR translocation from nucleus to cytoplasm is also involved. The mechanism through which vitamin D modulates response to glucocorticoids remains to be fully delineated.

Discussion
General Secretariat for Research and Technology.
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OC5.3
Activators of AMP-activated protein kinase regulate adipocyte aldosterone secretion and mineralocorticoid receptor signalling
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The increasing global prevalence of obesity requires urgent intervention to limit the anticipated surge of associated cardiometabolic morbidity and mortality. The energy sensor AMP-activated protein kinase (AMPK) is one proposed target for treating metabolic disorders and is downregulated in adipose tissue of obese insulin resistant individuals. Given the strong relationship between metabolic syndrome and overactivity of the renin-angiotensin-aldosterone system (RAAS) we investigated the role of AMPK in regulating adipocyte RAAS and mineralocorticoid receptor (MR) signalling. In vitro studies were carried out using differentiated 3T3-L1 (mouse) and SW872 (human) adipocytes. AMPK activators AICAR (1 mM) and A769662 (300 µM) were applied for 8 or 24 h. RT-PCR, immunoblotting and ELISA were used to assess effects on components of the renin-angiotensin-aldosterone system. Angiotensinogen, angiotensin II type 2 receptor and mineralocorticoid receptor mRNA levels were upregulated in differentiated adipocytes compared to undifferentiated fibroblasts. Aldosterone secretion by 3T3-L1 adipocytes and SW872 adipocytes was increased by 8 h of incubation with AICAR or A769662 respectively. Expression of Steroidogenic Acute Regulatory (StAR) mRNA was upregulated in accordance with aldosterone secretion along with associated down-regulation of MR mRNA and protein. Furthermore, we examined downstream MR targets serum and glucocorticoid-regulated kinase 1 (SGK1) and Lipocacin 2 which were both upregulated despite decreased MR. Interestingly, cells which produced aldosterone in response to AMPK activators exhibited a severe down-regulation of AMPK protein levels by 24 h. These data suggest that AMPK acts to control RAAS activity in adipocytes. We hypothesise that prolonged AMPK hyperactivation in vitro results in AMPK depletion allowing aldosterone secretion with subsequent increase in MR signalling. The upregulation of RAAS previously reported in obesity may be partially explained by the downregulation of AMPK related to excess nutrition.

Disclosure
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OC5.4
Adipose tissue-specific androgen generation fuels an adverse metabolic phenotype in patients with polycystic ovary syndrome
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Insulin resistance and androgen excess are the cardinal features of polycystic ovary syndrome (PCOS). The severity of hyperandrogenism and metabolic dysfunction in PCOS are closely correlated, but underlying mechanisms remain poorly understood. Alkidetoreductase type 1C3 (AKR1C3) is an important source of adipose androgen generation, activating androstenedione to testosterone (T). We postulated that AKR1C3 plays a critical role linking androgen metabolism and metabolic phenotype in PCOS.

We undertook in vivo deep phenotyping in ten women with PCOS and ten age/BMI-matched controls. Patients underwent oral challenge with 100mg of the androgen precursor dehydroepiandrosterone, with serum sampling every 30 min for 4 h and concomitant adipose microdialysis. Serum and adipose microdialysate androgens were measured by LC/MS. In complementary ex vivo and in vivo studies, we investigated adipose androgen generation, employing primary cultures of human adipocytes and the preadipocyte cell line 3G8S. The impact of androgens upon adipose lipid metabolism was assessed through measurement of de novo lipogenesis, free fatty acid uptake (FFA) and β-oxidation. After oral DHEA, area under the curve for serum T was higher in PCOS patients than controls, suggesting enhanced AKR1C3 activity. 5α-dihydrotestosterone (DHT) was detectable in adipose interstitial fluid and was higher in PCOS than controls, supporting adipose testosterone accumulation.

Subcutaneous adipose AKR1C3 mRNA expression correlated strongly with BMI. In human adipocytes, insulin up-regulated AKR1C3 expression and activity, while T increased de novo lipogenesis; both T and DHT increased FFA uptake and suppressed β-oxidation. Here we provide deep in vivo, ex vivo, and in vitro evidence that hyperinsulinaemia may drive adipose androgen generation through increased AKR1C3 expression and activity. This may have consequences for adipocyte function by driving lipid accumulation. Resultant adipocyte hypertrophy in PCOS could lead to increased insulin resistance, fuelling a vicious circle of hyperinsulinaemia, adipose androgen generation and increased lipid accumulation.

Disclosure
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OIC5.5
Pituitary hormone secretion profiles in IGSF1 deficiency syndrome
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Context
Loss-of-function of immunoglobulin superfamily 1 (IGSF1) causes an X-linked syndrome of central hypothyroidism, macroorchidism, and variable prolactin deficiency, GH deficiency in childhood, delayed pubertal testosterone rise, and/or obesity. The clinical features adver towards a pivotal role for IGSF1 in the pituitary gland, but detailed knowledge on pituitary hormone secretion in this syndrome is lacking.

Objective
To study detailed 24 h spontaneous pituitary hormone secretion in patients with the IGSF1 deficiency syndrome.

Methods
We performed a 24 h sampling study with measurements every 10 min in eight IGSF1 deficient patients. Deconvolution, modified cosinor, and approximate entropy (ApEn) analyses were applied to quantify TSH, prolactin, and gonadotropin secretion rates, diurnal rhythmicity, and regularity of hormone release. Results were compared to matched healthy controls or (for TSH) patients with subclinical primary hypothyroidism (SCH).

Results
Compared to both healthy controls and SCH, IGSF1 deficient patients showed decreased pulsatile secretion of TSH with decreased disorderliness and absence of diurnal variation. Basal and pulsatile secretion of FSH was increased, while LH secretion was not different from healthy controls. For prolactin secretion, two phenotypes were observed, with absence of prolactin secretion in some and increased basal and total prolactin secretion in others.

Conclusion
The TSH secretion pattern is consistent with the previously proposed hypothesis of defective TRH signalling in IGSF1 deficiency, which is further supported by a decreased TSH response to TRH in patients, and the decreased expression of pituitary Tbrh mRNA in IGSF1 knock-out mice. However, the increased FSH and prolactin secretion, but normal LH secretion, in combination with the delayed puberty despite normal testicular growth, have been observed in untreated primary hypothyroidism, and provoke some novel hypotheses.

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The endogenous thyroid hormone metabolite 3,5-diiodothyronine (3,5-T2) has attracted attention as a metabolically active substance modulating metabolism via classical thyroid hormone (TH) receptor-dependent and rapid plasma membrane, cytosolic and mitochondrial signaling pathways. Accordingly, 3,5-T2 has been proposed as a potential hypolipidemic agent without inducing thyromimetic effects and is frequently used as illicit weight-reducing agent. The objective of the present study was to investigate 3,5-T2 effects on energy and lipid metabolism in a mouse model of diet-induced obesity. Adult male mice received either 3,5-T2 (2.5 μg/kg bw) or saline i.p. over 28 days. Contrary to our expectations the heart weight strongly increased by 26 percent with 3,5-T2 treatment. Because only limited data are currently available about 3,5-T2 effects on heart, we started to investigate the potential role of 3,5-T2 in cardiac remodeling and hypertrophy.

The results in 3,5-T2 exposed heart tissue indicate that 3,5-T2 modulates expression of TH responsive cardiac genes. The gene expression of Ca++-ATPase (Serca2a2) was significantly increased while protein and gene expression of the Ca++-ATPase inhibitor phospholamban was decreased. Interestingly, 3,5-T2 application enhanced transcript concentration of myosin heavy chain (Myh7) and reduced the mRNA concentration (Myh7) was significantly increased while protein and gene expression of the Ca++-ATPase inhibitor phospholamban was decreased. Accordingly, 3,5-T2 has been proposed as a potential hypolipidemic agent without inducing thyromimetic effects and is frequently used as illicit weight-reducing agent. The objective of the present study was to investigate 3,5-T2 effects on energy and lipid metabolism in a mouse model of diet-induced obesity. Adult male mice received either 3,5-T2 (2.5 μg/kg bw) or saline i.p. over 28 days. Contrary to our expectations the heart weight strongly increased by 26 percent with 3,5-T2 treatment. Because only limited data are currently available about 3,5-T2 effects on heart, we started to investigate the potential role of 3,5-T2 in cardiac remodeling and hypertrophy.

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establishment of a clear diagnosis in 15–30% of cases (mainly follicular lesions). Molecular biology techniques can be useful, allowing for the detection, in FNACC smears, of the known mutations involved in the oncogenesis. 

Aim

to evaluate the usefulness of the detection of the BRAF mutation in FNAC in the early diagnosis of TC.

Material and methods

The study involved 1590 consecutive patients examined for 2 years and 2290 FNACC were performed. The FNAC results were classified according to the Bethesda system. In the case of the cytological results group 3,4,5 the molecular analysis was performed in order to detect BRAF mutation using the combination of Sanger sequencing, ASA-PCR and qPCR techniques. All the patients with BRAF mutation were operated on.

Results

Out of 2290 FNACC in groups 3,4,5 there were classified 106,29,12 respectively. Molecular analysis showed the presence of the BRAF mutation in a total of 12 cases (8.2%): three positive cyt pathological results out of 106- in group 3, 0 out of 29 in group 4, and 9 positive out of 12- in group 5. Histopathological studies confirmed the presence of PTC in all the 12 patients with BRAF mutation present. Conclusions

The presence of BRAF mutation in FNACC material is always associated with the presence of PTC, however from the clinical point of view the confirmation of the presence of mutations is of little help in early diagnosis. Revealing the BRAF mutation has resulted in a change of procedure only in the case of three patients, with pathological proven PTC. These were cases from group 5 – the cytology procedure was enough to indicate those patients eligible for surgery.

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OC6.5

Search for new candidate genes in RET mutation-negative families with hereditary medullary thyroid carcinoma using next generation sequencing

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Introduction

Hereditary medullary thyroid carcinoma (MTC) is associated with only one major cause – germline mutations in the RET proto-oncogene. The most tested families with MTC is related to specific RET mutation, however, very small number of families left unresolved without the causing inherited mutation. New techniques of next generation sequencing give hope in finding the new candidate genes that could be involved in the pathogenesis of these MTC families.

Methods

We performed RET genetic screening in 870 individuals - 490 patients and 380 at-risk relatives. The germline RET mutation was detected in 58 families (83% of familial and 7% of apparently sporadic MTCs). No mutation in all RET exons was found in six families with clinically supposed hereditary form of MTC (4 FMTC and 2 MEN2A phenotype). Six index patients of these families were analyzed using TruSight Cancer Sequencing Panel (Illumina) that targeted 94 genes associated with cancer. After exclusion of common single nucleotide polymorphisms, the data were focused on novel or rare non-synonymous variants in coding sequences and tested in silico (SIFT, PolyPhen) for possible damaging effect.

Results

Several promising variants in each patient have been identified in genes involved in key processes for cancer development such as repair genes. Considering SIFT and PolyPhen evaluation, the analysis has discovered very rare variants in genes RHBDF2, XPA, MET and CHEK2. The variants detected in APC and EZH2 were previously investigated in association with other cancers. Three patients have a pathogenic polymorphism in HNF1A.

Conclusion

New candidate genes can represent genetic modifying factors or crucial genes in each family. Although detected alterations are promising, it is necessary to verify them in other affected family members.

Disclosure

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OC7.1

Genetic screening of regulatory regions of pituitary transcription factors among patients with idiopathic pituitary hormone deficiencies

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Introduction

POU1F1 is a pituitary transcription factor, critical for differentiation of pituitary somatotrophs, thyrotrhops and lactotrophs. POU1F1 expression depends on the presence of PRO1, which attenuates expression of transcriptional repressor HESX1. Previous mutation screening of POU1F1 coding exons in our cohort of patients with combined pituitary hormone deficiency (CPHD) showed POU1F1 mutations in only 1% of the families. We hypothesised that defects in the regulatory region of POU1F1 might explain the phenotype of CPHD.

Patients and methods

We screened the regulatory regions of POU1F1, as well as those of PRO1 and HESX1 among 87 patients with CPHD (62M/25F). Since patients with HESX1 mutations can initially present with IGHD only, we also screened 92 patients with IGHD (64M/28F). We compared genotype frequencies in our CPHD cohort with those found in controls from the 1000 genomes project and we studied PRO1 and POU1F1 promoter SNPs in relation to phenotypic data.

Results

We found a new variant in the POU1F1 promoter. We are currently performing promoter-luciferase reporter assays, since in silico analysis of the new variant showed potential effects on promoter activity by creating a new binding site for several transcription factors. In addition, we found two known SNPs in the POU1F1 promoter and six known SNPs in the PRO1 promoter. We did not find any variant in the HESX1 promoter. Rs148607624, a three nucleotide deletion in the PRO1 promoter which has previously been associated with CPHD, showed a relation with IGF1 levels in our CPHD patients.

Conclusion

We screened the regulatory regions of pituitary transcription factors POU1F1, PRO1 and HESX1 in our cohort of CPHD patients and found a new variant in the POU1F1 promoter region. We will present detailed phenotypic data of the patient carrying the new variant. We will show the impact of the new variant on POU1F1 promoter activity.

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OC7.2

KLF4 in hypothalamus regulates leptin homeostatic effects through AgRP

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Introduction

Krupel-like factor 4 (KLF4) is a zinc-finger-type transcription factor expressed in a range of tissues that plays multiple functions. KLF4 expression is found in neural stem cells and is critical to neuronal differentiation. Recent evidence suggests that KLF4 also plays an important role in the central regulation of energy balance.

In vitro studies show that KLF4 is a transcriptional regulator of agouti-related protein (AgRP), essential to the hyperphagic response.

Description of methods/design


Results

We report that hypothalamic KLF4 represents a new transcription factor specifically modulating agouti-related protein (AgRP) expression in vivo.

DOI: 10.1530/endoabs.37.OC7.2
Hypothalamic KLF4 colocalises with AgRP neurons and is modulated by nutritional status and leptin. Over-expression of KLF4 in the hypothalamic arcuate nucleus (ARC) induces food intake and increases body weight through the specific stimulation of AgRP, as well as blunting leptin sensitivity in lean rats independent of forkhead box protein 1 (FoxO1). Down-regulation of KLF4 in the ARC inhibits fasting-induced food intake in both lean and diet-induced obese (DIO) rats. Silencing KLF4, however, does not, on its own, enhance peripheral leptin sensitivity in DIO rats.

Conclusion

i) Hypothalamic KLF4 is regulated by leptin through both STAT3 and PI3K signalling pathways. ii) KLF4 over-expression in the ARC is sufficient to increase food intake and to blunt the anorectic action of leptin in a FoxO1-independent manner. iii) Leptin fails to inhibit hypothalamic KLF4 expression in DIO rats, while KLF4 does not on its own regulate HFD-induced peripheral leptin resistance.

Disclosure


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OC7.3

Maternal distress associates with placental genes regulating foetal glucocorticoid exposure and IGFB2: role of obesity and sex

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Introduction

Maternal distress, including poorer life satisfaction, increased anxiety and depression (A&D) symptoms, are worse in Severely Obese (SO) than lean pregnancy and may alter placental genes regulating foetal glucocorticoid exposure and placental growth. We hypothesised that the associations between increased maternal distress with changes in placental mRNA levels leading to a reduced placental barrier to maternal glucocorticoids, and altered placental IGFB2, are more pronounced in SO pregnancy. We also considered any sex-specific effects.

Methods

Placental mRNA levels of genes regulating glucocorticoid including 11β-HSDs, NR3C1, NR3C2, ABC transporters, mTOR and IGFB2 family were measured in term placental samples from 43 lean (BMI ≤25 kg/m2) and 50 SO (BMI ≥40 kg/m2) women, in whom A&D symptoms were prospectively evaluated during pregnancy.

Results

The mRNA levels of genes with a similar role in regulating foetal glucocorticoid exposure were strongly inter-correlated (all 0.29 ≤ P ≤ 0.7, P ≤ 0.05). Increased A&D symptoms associated with increased NR3C2 and IGFB2 in both lean and SO group (all 0.3 ≤ P ≤ 0.05). Increased maternal distress was associated with higher ABCB1 and ABCG2 mRNA levels in SO but lower ABCB1 and higher 11β-HSD1 mRNA levels in lean (all P ≤ 0.05) suggesting a protective adaptive response in SO placentas. Increased maternal distress associated with reduced mRNA levels of ABCB1, ABCG2, 11β-HSD2, NR3C1and IGFB2 in female placentas (all ≤ 0.29, P ≤ 0.05), but not in males.

Conclusion

The observed sex differences in placental responses suggest greater vulnerability of female foetuses to maternal mood with potentially greater fetal glucocorticoid exposure and excess IGFB2. Further studies are needed to test whether this translates to potentially greater negative outcomes of maternal distress in females in early childhood.

Disclosure

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OC7.4

Gonadotropin-inhibitory hormone signalling displays sexually dimorphic roles in the control of energy homeostasis: studies in the NPFF1 receptor null mouse

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RF-amide-related peptide-3 (RFRP-3), the mammalian orthologue of the avian gonadotropin-inhibiting hormone (GnIH), has been proposed as major inhibitory signal for the reproductive axis, acting via the NPFF1 receptor (NPFF1R). In addition, RFRP-3 has been recently suggested to modulate feeding, with reported orexigenic actions; a function that might contribute to the integrative control of energy homeostasis and reproduction. However, characterisation of the metabolic effects of RFRP-3/GnIH signalling remains superficial and largely restricted to few pharmacological studies. As a means to address the putative physiological roles of GnIH/RFRP-3 signalling in the control of metabolic homeostasis, we report here the metabolic phenotyping of the first mouse line with constitutive inactivation of NPFF1R. Congenital elimination of NPFF1R did not alter adult body weight (BW) neither affected BW responses to high fat diet (HFD) in males. In contrast, NPFF1R KO null female mice tended to be slightly heavier and displayed exaggerated BW increases in response to obesogenic insults, such as HFD or ovariectomy. Conversely, NPFF1R KO males, but not females, fed on HFD showed perturbed glycaemic responses in glucose tolerance tests, even though basal glucose and insulin concentrations were not significantly different from WT levels. In addition, the patterns of food intake were affected in NPFF1R KO of both sexes, with modest decreases in acute food intake and altered responses to leptin and ghrelin; feeding suppression following leptin administration was exaggerated in NPFF1R null mice, while the orexigenic responses to ghrelin were partially blunted in the absence of NPFF1R signalling. In sum, we provide herein the metabolic characterization of a mouse model of congenital elimination of the canonical receptor for GnIH/RFRP-3. While our data are compatible with a (modest) role of GnIH/RFRP-3 as orexigenic factor that mediates part of the effects of ghrelin on food intake, our study is the first to disclose the deleterious metabolic impact of concurrent obesogenic insults, such as HFD, in a sexually dimorphic manner.

Disclosure

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OC7.5

Not so giants: mice lacking both somatostatin and cortistatin have high GH levels, but show no changes in growth rate or IGF-I levels

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Somatostatin (SST) and cortistatin (CORT) are two highly related neuropeptides involved in the regulation of several endocrine secretions. In particular, SST and CORT are two primary negative regulators of GH secretion. Consequently, SST or CORT knockout (KO) mice exhibit elevated GH levels; however, this does not lead to increased IGF-I levels or somatic growth, which has been suggested that
could be due to a compensatory mechanism between both peptides. In order to test this hypothesis, this study was designed to explore, for the first time, the consequences of simultaneously deleting endogenous SST and CORT by generating a double SST/CORT KO mouse model and exploring its endocrine and metabolic phenotype. Our results demonstrate that simultaneous deletion of SST and CORT induces a drastic elevation of endogenous GH levels, which, surprisingly, does not lead to increased growth rate or IGF-I levels, suggesting the existence of additional factors/systems that, in the absence of endogenous SST and CORT, could counteract GH-actions. Notably, elevation in circulating GH levels are not accompanied by changes in pituitary GH expression or by alterations in the expression of its main regulators (GHRIH and ghrelin) or their receptors (GHRHR-R, GHS-R or SST/CORT receptors) at the hypothalamic or pituitary level. However, although double SST/CORT KO male mice exhibit normal glucose and insulin levels, they have improved insulin sensitivity compared to control mice. Therefore, these results suggest the existence of an intricate interplay among the known (SST/CORT), and likely unknown, inhibitory components of the GHGHF-I axis to regulate somatic growth and glucose/insulin homeostasis.

Endocrine tumours

OC8.1

A role for vault particles as a marker for therapeutic effects against endocrine tumours
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The vault complex, consisting of a major vault protein (MVP), two minor vault proteins (VPARP and TEP1) and small untranslated RNA molecules (vault RNAs 1–4), is considered the largest intracellular ribonucleoprotein particle. Although in recent years, vaults were believed to be involved in multidrug resistance, the exact function of this complex has remained unclear. Recently, we investigated the therapeutic applicability of a Tumour-Vascular-Disrupting Agent (ASA) in preclinical models for neuroendocrine tumours of the gastroenteropancreatic system (BON) and adrenocortical carcinoma (NCIh295R). Upon treatment we detected highly significant anti-tumoural effects in BON xenografts which were not evident in NCI-H295R. In an attempt to explain differences in therapeutic responses, gene expression patterns within these tumours were investigated by a gene array. Subsequent analyses identified vault RNAs 1–3 as the most pronounced regulated transcripts in the tumour model showing therapeutic responsiveness. Quantitative real time PCR confirmed these results for ASA treated BON tumours (% of 100% controls; vault1: 2484.1 ± 367.9%, P < 0.001; vault2: 1922.5 ± 235%, P < 0.001; vault3: 901.3 ± 119%, P < 0.001) while no changes were detectable for the non-responding NCI-H295R xenografts (% of 100% controls; vault1: 224.1 ± 84.8%, P > 0.05; vault2: 113 ± 23%, P > 0.05; vault3: 89.5 ± 14%, P > 0.05). Subsequently, we investigated NCI-H295R-xenografts which had been treated with two different chemotherapeutic regimens (EDP-M and LEDP-M). In this therapeutic setting treatment-dependent upregulation of vault RNAs could also be detected in NCI-H295R-tumors (% of 100% controls; vault1: EDP-M 296 ± 3.4%, P < 0.001; LEDP-M 243.5 ± 16%, P < 0.001; vault2: EDP-M 157.2 ± 20%, P < 0.05; LEDP-M 160.7 ± 20%, P < 0.05; vault3: EDP-M 241.2 ± 55%, P < 0.001; LEDP-M 118.9 ± 16%, P < 0.05). Further in vitro analyses revealed dynamic changes in vault RNA expression also upon blastidicin, doxorubicin, mitotane treatment and a significant increase in MVP protein levels upon TNP alpha treatment in BON cells. In summary, further investigation and modulation of vault particles might have potential to improve efficacy of anticancer drugs in endocrine tumours.

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OC8.2

Role of microenvironment on neuroblastoma SK-N-AS SDHB silenced cell metabolism and function
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Solid tumours are very complex tissues comprising not only cancer cells, but also non-malignant stromal cells such as endothelial cells, fibroblasts, immune cells and extracellular matrix, forming the so called tumour microenvironment. In the last few years, it has become more and more evident the pivotal role of the tumour microenvironment in modulating cancer progression and metastasis. Tumour microenvironment has thus become a potential therapeutic target. To obtain an experimental model resembling the in vivo conditions of the succinate dehydrogenase B subunit (SDHB)-mutated paragangliomas (PGL), we evaluated the effects of SDHB silencing on metabolism and proliferation in the human neuroblastoma cell line (SK-N-AS), cultured alone or in association with human fibroblasts. Silencing, verified by Western Blot and densitometry analysis, caused a 70% decrease in protein expression, an almost complete loss of the complex specific enzymatic activity and a significant increase in HIF1α and HIF2α expression, thus resembling the in vivo tumour cell phenotype. When compared to wild type SK-N-AS cells, SDHB silenced cells showed an altered metabolism characterised by an unexpected significant decrease in glucose uptake and by an increase of lactate uptake. Moreover, silenced cells showed a significant increase in cell proliferation and metalloproteinase activity. When co-cultured with human fibroblasts, control cells showed a significant decrease in glucose uptake and a significant increase in cell proliferation vs their mono-cultured counterparts. These effects were even more strikingly evident in co-cultured silenced cells which showed a 70% decrease in glucose uptake and a 92% increase in cell proliferation vs their mono-cultured counterparts. Our data demonstrate, for the first time, that SDHB impairment causes a metabolic and functional derangement of neural crest-derived tumour cells and that microenvironment, here represented by fibroblasts, strongly affects their tumour metabolism and growth capacity.

Disclosure
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OC8.3

miR-372 is aberrantly expressed in most parathyroid tumours and might contribute to parathyroid tumourigenesis by inhibiting CDKN1A/p21 and LATS2
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We previously described aberrant expression of microRNAs belonging to the chromosome 19 cluster (C19MC) and the close miR-371-373 cluster in two-thirds of parathyroid carcinomas (PCa). Therefore, we investigated the involvement of the miR-371-373 cluster in parathyroid tumours, where miR-372 was the most consistently upregulated. miR-372 is known to be highly expressed in human

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embryonic stem cells and definitely downregulated upon differentiation. Moreover, miR-372 promotes human somatic cell reprogramming. miR-372 was expressed at high levels (more than fourfold) in 48 out of 79 parathyroid tumours compared with the expression levels in normal parathyroid glands \((n=5)\). miR-372 was expressed in more than 50% of both atypical parathyroid adenomas (PAs; \(n=18\); 5.9 ± 0.8-fold, \(P=0.003\)) and PCAs \((n=15); 5.1 ± 1.1\)-fold, \(P=0.01\)) at levels significantly higher than those in typical PAs \((n=46); 2.1 ± 0.7\)-fold). miR-372 overexpression in HEK293 and MCF7 cells significantly downregulated mRNA and protein levels of the cyclin inhibitor kinase CDKN1Ap21 and of the large tumour suppressor kinase 2 (LATS2). Similarly, CDKN1A and LATS2 mRNA levels were significantly downregulated by the miR-372 overexpression in typical PAs-derived cells. miR-372 overexpression attenuated the GoG1 checkpoint in the cell cycle, reducing the proportion of cells in the GoG1 phase from 70 to 59%. Furthermore, miR-372 has been related with the ‘stemness’ Wnt/b-catenin signalling pathways. In 16 typical PAs we found that miR-372 levels were positively correlated with the nuclear b-catenin accumulation, investigated by western blot, and with the mRNA levels of the direct gene target of nuclear b-catenin transcriptional activity AXIN2. Nonetheless, in typical PAs-derived cells \((n=6)\) miR-372 expression levels were not affected by lithium chloride-induced nuclear b-catenin accumulation. In conclusion, i) miR372 was aberrantly expressed in a subset of parathyroid tumours; ii) atypical PAs and PCAs expressed miR-372 more frequently and at higher levels than typical PAs; iii) CDKN1Ap21 and LATS2 were targets of miR-372 inhibitory effects in PAs-derived cells; iv) miR-372 aberrant expression might impair Wnt/b-catenin pathway in parathyroid tumour cells.

**Disclosure**

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**OC8.5**

Oestrogen receptor \(\alpha\) promotes prostate cancer progression through dual actions in both epithelia and stroma

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The effects of peptides with oestrogen-like activity on cell proliferation and on energy metabolism in human derived tumour cell lines

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Oestradiol-17\(\beta\) regulates diverse tissues and cells, both within and outside the reproductive system including human cancer cells. Currently used ERs agonists or antagonists are synthetic compounds prepared by structure modifications. Alternatively, peptide mimics of steroids would allow preparation of biased combinatorial libraries of chemical and biological origin, from which estrogenic or antagonists are synthetic compounds prepared by structure modifications. Here we report the development of peptides with tissue selective profiles can be selected. The phage-display peptide library may offer a suitable way to obtain peptides that mimic E2 biological activity. These libraries are diverse collections of random peptides displayed on the surface of filamentous phages, which can be screened for binding to a target molecule, such as an antibody or receptor. These combinatorial peptide libraries have not been used to isolate peptides that mimic the activity of organic compounds such as steroids. Here we report the development of peptides with oestrogen-like activity. We employed a novel approach utilizing a monoclonal antibody against oestradiol (mAb E2-15) to screen a 15-mer phage-display peptide library and to affinity select phage that interacted with mAb E2-15. Synthesis of such peptides resulted in the identification of a 15-mer linear peptide which interacted specifically with mAb E2-15. Incorporation of flanking residues at the N-terminus and the C-terminus of the peptide, resulted with peptides recognized specifically by mAb E2-15 and ER\(\alpha\). The peptides A44 (KAWFPE), A45 (KRPAFFE), EMP-1 (VSYWFPEE), EMP-2, and cyclic peptide (23mer) stimulated DNA and CK in ‘endocrine’ and ‘non-endocrine’ human cancer cell lines. In ovarian cancer A2780, only EMP1 and EMP2 induced CK whereas 23mer inhibited it. In prostate cancer C4-24 CK was induced by all peptides tested. In colon cancer 320D, CK was induced by all except EMP2 and in adrenal carcinoma H295R all peptides except EMP1 stimulated CK. In A2780 DNA was stimulated by EMP1 and EMP2 but inhibited by A44 and mer23. In C4-24 and in 320D all peptides except EMP2 stimulated DNA. In H295R DNA synthesis was stimulated by all peptides except EMP1. All cells tested expressed ER\(\alpha\), ER\(\beta\) and VDR to different levels. These mRNAs were variably affected by oestrogens. In conclusion, some of these peptides can be lead compounds for the effects on human cancer cells and might be targets for chemical modifications leading to development of inhibitors of growth of these cancer cells.

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**OC8.4**

The effects of peptides with oestrogen-like activity on cell proliferation and on energy metabolism in human derived tumour cell lines

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Oestradiol-17\(\beta\) regulates diverse tissues and cells, both within and outside the reproductive system including human cancer cells. Currently used ERs agonists or antagonists are synthetic compounds prepared by structure modifications. Alternatively, peptide mimics of steroids would allow preparation of biased combinatorial libraries of chemical and biological origin, from which estrogenic peptides with tissue selective profiles can be selected. The phage-display peptide library may offer a suitable way to obtain peptides that mimic E2 biological activity. These libraries are diverse collections of random peptides displayed on the surface of filamentous phages, which can be screened for binding to a target molecule, such as an antibody or receptor. These combinatorial peptide libraries have not been used to isolate peptides that mimic the activity of organic compounds such as steroids. Here we report the development of peptides with oestrogen-like activity. We employed a novel approach utilizing a monoclonal antibody against oestradiol (mAb E2-15) to screen a 15-mer phage-display peptide library and to affinity select phage that interacted with mAb E2-15. Synthesis of such peptides resulted in the identification of a 15-mer linear peptide which interacted specifically with mAb E2-15. Incorporation of flanking residues at the N-terminus and the C-terminus of the peptide, resulted with peptides recognized specifically by mAb E2-15 and ER\(\alpha\). The peptides A44 (KAWFPE), A45 (KRPAFFE), EMP-1 (VSYWFPEE), EMP-2, and cyclic peptide (23mer) stimulated DNA and CK in ‘endocrine’ and ‘non-endocrine’ human cancer cell lines. In ovarian cancer A2780, only EMP1 and EMP2 induced CK whereas 23mer inhibited it. In prostate cancer C4-24 CK was induced by all peptides tested. In colon cancer 320D, CK was induced by all except EMP2 and in adrenal carcinoma H295R all peptides except EMP1 stimulated CK. In A2780 DNA was stimulated by EMP1 and EMP2 but inhibited by A44 and mer23. In C4-24 and in 320D all peptides except EMP2 stimulated DNA. In H295R DNA synthesis was stimulated by all peptides except EMP1. All cells tested expressed ER\(\alpha\), ER\(\beta\) and VDR to different levels. These mRNAs were variably affected by oestrogens. In conclusion, some of these peptides can be lead compounds for the effects on human cancer cells and might be targets for chemical modifications leading to development of inhibitors of growth of these cancer cells.

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Adrenal 2

OC9.1

Effects of dexamethasone and adrenocorticotropin on circulating microRNA expression in humans
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Objective

MicroRNAs are short non-protein coding RNA molecules involved in the regulation of numerous homeostatic processes via modulating gene expression. There are some data that the expression of microRNA might be modulated by hormones, but the interaction of hormones and circulating microRNAs of adrenocortical origin is mostly unknown.

Methods

The expression of six selected circulating microRNAs (hsa-miR-27a, hsa-miR-125b-2, hsa-miR-200b, hsa-miR-214, hsa-miR-483-5p, hsa-miR-503) was studied in plasma samples of ten individuals examined by 1 mg dexamethasone suppression test and another ten individuals stimulated by 250 µg tetracosactide (adrenocorticotropin). Total RNA was isolated from plasma samples and microRNA expression has been analysed by Tagman RT-qPCR normalized to cel-miR-39 as reference. The expression of hsa-miR-27a was also studied in vitro in NCI-H295R adrenocortical cell line.

Results

From the six circulating microRNAs selected for the in vivo study based on literature data showing their association to adrenocortical cancer or their responsiveness to hormonal stimuli in animal models, only circulating hsa-miR-27a proved to be significantly modulated in vivo: its expression was up-regulated by dexamethasone whereas it was suppressed by adrenocorticotropin. Expression of secreted hsa-miR-27a was significantly induced in culture supernatants of NCI-H295R cells, as well.

Conclusions

hsa-miR-27a expression is modulated by hormones of the hypothalamic-pituitary-adrenal axis both in vitro and in vivo. Dexamethasone induced secreted hsa-miR-27a both in vitro and circulating hsa-miR-27a in vivo. The expression of circulating hsa-miR-483-5p proposed as diagnostic marker for adrenocortical malignancy was not affected by dexamethasone or tetracosactide administration supporting its usefulness for the evaluation of malignancy of adrenocortical lesions.

Disclosure

Hungarian Scientific Research Grant (OTKA K100295 to Peter Igaz; OTKA Disclosure support for its usefulness for the evaluation of malignancy of adrenocortical malignancy was not affected by dexamethasone or tetracosactide administration of circulating hsa-miR-483-5p proposed as diagnostic marker for adrenocortical malignancy was not affected by dexamethasone or tetracosactide administration.

OC9.2

Alternative pathway synthesis dominates androgen production in patients with congenital adrenal hyperplasia and is decreased by Chronocort® more than by conventional glucocorticoid therapy
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Introduction

Twenty-four hour urinary steroid excretion was analysed at baseline on different days after dexamethasone suppression. The expression of six selected circulating microRNAs (hsa-miR-27a, hsa-miR-200b, hsa-miR-214, hsa-miR-483-5p, hsa-miR-503) was studied in plasma samples of ten individuals examined by 1 mg dexamethasone suppression test and another ten individuals stimulated by 250 µg tetracosactide (adrenocorticotropin). Total RNA was isolated from plasma samples and microRNA expression has been analysed by Tagman RT-qPCR normalized to cel-miR-39 as reference. The expression of hsa-miR-27a was also studied in vitro in NCI-H295R adrenocortical cell line.

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Disclosure

Hungarian Scientific Research Grant (OTKA K100295 to Peter Igaz; OTKA Disclosure support for its usefulness for the evaluation of malignancy of adrenocortical malignancy was not affected by dexamethasone or tetracosactide administration.

OC9.3

Modelling the salivary cortisone to serum cortisol inter-relationship to predict serum cortisol under physiological conditions and after hydrocortisone
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Introduction

Measuring serum cortisol to evaluate the normal circadian rhythm and adequacy of hydrocortisone replacement levels requires multiple readings; an expensive, cumbersome process. Conversely, salivary cortisone, a surrogate marker for free cortisol levels is non-invasive and well suited for out-patient settings. We hypothesised that salivary cortisone predicts circulating cortisol levels and can be used as an alternative marker of serum cortisol in a physiological setting or in patients on hydrocortisone replacement.

Methods

This was an observational study in 14 healthy male volunteers who had hourly serum cortisol measurements over 24 h in addition to salivary cortisol and cortisone measurements from 1500 h to 2200 h and from 0700 h to 1500 h; all measurements were carried out by liquid chromatography/random mass spectrometry. Relationships between serum and salivary cortisol/cortisone were assessed by individual correlation analysis and linear mixed effects modelling. A similar analysis was carried out after 20mg of oral and i.v. hydrocortisone given on different days after dexamethasone suppression.

Results

Correlation analysis (r), for the relationship between endogenous log-transformed salivary cortisone or salivary cortisol with serum cortisol rhythm, ranged from 0.96 to 0.99; P <0.001 and from 0.84 to 0.99; P <0.001, respectively. Salivary cortisol was superior to serum cortisol (range R², 0.93–0.99 vs 0.71–0.97) in predicting circulating, serum cortisol. By fitting a mixed effects model to predict serum cortisol levels from salivary cortisone (predicted serum cortisol (nmol/l) = (13.57 + individual-specific random effects) × salivary cortisone (nmol/l)) correlation r and R² between measured and predicted serum cortisol were 0.91 and 0.82 under physiological conditions, 0.89 and 0.66 for 20 mg oral hydrocortisone and 0.93 and 0.72 for 20 mg i.v. hydrocortisone, respectively.

Conclusion

Salivary cortisol levels are strongly related to serum cortisol and repetitive measurements of salivary cortisone may be used to predict the serum cortisol rhythm and cortisol levels after hydrocortisone.

Disclosure

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OC9.4

More than 2.5-fold increased risk for adrenal crises in patients with Addison’s disease and the autoimmune polyglandular syndrome compared with secondary adrenal failure: German health insurance data 2010–2013

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Introduction

Adrenal crises are potentially life-threatening complications in patients with adrenal insufficiency (AI). Our objective was to investigate the frequency of adrenal crises in patients with different forms of AI in the Techniker Krankenkasse (TK), one of the largest German Health Insurance providers, covering more than 12% of the German population.

Design

The Statutory Health Insurance (SHI) database of the TK was analysed for diagnostic codes over an observation period from 01.01.2010 to 31.12.2013. Adjusting data for age and sex, n = 11691 diagnoses of AI were recorded and classified in primary (n = 4231), respectively secondary (n = 7460) AI. Additionally, the subgroup with autoimmune polyglandular syndrome (APS) comprising AI was defined (n = 1487). A query for ICD-code E27.2 (adrenal crisis) was performed in these cohorts.

Results

In our cohort, we found a prevalence of 222/million for secondary and 126/million for primary AI. Adrenal crises were documented with a frequency of 4.8/100 patient years. Crises were significantly more frequent in patients with primary (7.6/100 patient years) compared to those with secondary AI (3.2/100 patient years; P < 0.0001). Prevalence of crises was higher in individuals with APS comprising primary AI (10.9/100 patient years) and highest in patients with primary AI and type 1 diabetes (12.5/100 patient years).

Conclusions

Applying the SHI database of the TK, comprising more than 8 million individuals, we identified profound data about the risk of adrenal crises in different groups of patients with AI. For the first time our data confirm and extend the clinical observation, that patients with primary AI and additional autoimmune endocrinopathies are at highest risk for adrenal crises. Approximately one of eight patients with primary AI and type 1 diabetes suffers from an adrenal crisis per year. These data provide a basis for specific targeting of efforts aiming at the prevention of adrenal crises.

Disclosure

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OC9.5

The Notch ligand Jagged1 is up-regulated in adrenocortical carcinomas and is associated with a favourable clinical outcome

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Background

Adrenocortical tumours consist of frequent adrenocortical adenomas (ACA) and highly malignant (ACC) with a still incompletely understood pathogenesis. Dysregulation of Notch signalling pathway is implicated in several cancers with oncogenic or tumour suppressor functions. Copy number gains and over-expression of Jagged1, a ligand of Notch receptor, was reported in ACC. The aim of the study was to evaluate the expression of Jagged1 and other Notch-related factors in adrenocortical tumours and to correlate it with clinical outcome.

Material and methods

mRNA expression of JAG1, NOTCH1, CTNNB1, and selected target genes of Notch signalling (HES1, HES5 and HEY2) and Wnt/β-catenin pathway (LEF1) was evaluated in 80 fresh frozen samples (28 normal adrenal glands = NAG, 24 ACA, 28 ACC) by quantitative real-time PCR. Immunohistochemistry was performed in 221 tissues on paraffin slides (16 NAG, 27 ACA, 178 ACC) for Jagged1, activated Notch1 (aNotch1) and HEY2 staining. The relationship with nuclear β-catenin expression was also investigated.

Results

mRNA expression of JAG1, NOTCH1, CTNNB1, and target genes was not significantly different between normal and neoplastic adrenal glands. At protein level, all factors evaluated were highly expressed (β-score 2–3) in a larger proportion of ACCs than in ACAs and NAG (Jagged1 in 27, 15 and 10% of NA, respectively, P = 0.0004; aNotch1 in 13%, 8% and none of NAG, P < 0.0001; HEY2 in 66, 61 and 33%, P = 0.0001). High Jagged1 expression was associated with earlier ENSAT tumour stage (P = 0.07) and lower number of metastases (P = 0.08) in ACC. Accordingly, high Jagged1 levels impacted favourably on overall survival (n = 168, 131 vs 30 months, P = 0.0023, HR = 0.45) and progression free survival (37 vs 9 months, P = 0.0023, HR = 0.51), even after adjustment for ENSAT tumour stage (P = 0.005) and nuclear β-catenin expression (P = 0.009).

Conclusion

Jagged1 is overexpressed in a subgroup of ACCs, being associated with a more differentiated phenotype and better clinical outcome. Notch1 signalling pathway activation might be involved in adrenocortical tumor progression, but still needs to be better investigated.

Disclosure

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Nuclear receptors and signalling

OC10.1

Resistin negatively regulates neutral adiponectin signalling through the down regulation of APPL1 and adiponectin receptors

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Obesity is linked to common metabolic diseases including insulin resistance, which constitutes a principal risk factor for type 2 diabetes. Increasing evidence indicates that changes in adipose-secreted factors in obesity, dramatically affect insulin sensitivity. Among these adipokines, resistin is described as a key factor in obesity-mediated both inflammation and insulin resistance. However, little is known about the molecular mechanisms mediating resistin effects particularly at the neuronal level. Recently, we have shown that central resistin acts by way of hypothalamic TLR4 receptors promoting overall inflammation and insulin resistance. Adiponectin is another adipokine with anti-diabetic and insulin sensitizing properties. A decrease in adiponectin level and action has been linked to insulin resistance. Here, we aim to investigate whether resistin could contribute to insulin resistance through the impairment of adiponectin action. To test this hypothesis we examined the impact of resistin overexposure on adiponectin signaling in human neuronal cells SH-SY5Y. Interestingly, we show that resistin treatment completely abolished adiponectin-dependent Akt phosphorylation whereas ERK1/2 was not affected. Importantly, resistin treated SH-SY5Y cells showed a marked down-regulation of adiponectin receptor (AdipoR1) and APPL1, a critical mediator of both adiponectin and insulin signaling. This has been confirmed in vivo. Indeed, in Wistar rats, chronic ICV resistin infusion (14 days) markedly reduced hypothalamic expression of APPL1 AdipoR1 and AdipoR2. Furthermore, to assess whether resistin action on adiponectin signalling is mediated by TLR4, we generated TLR4-depleted SH-SY5Y cells. Interestingly, the knock-down of TLR4 completely abrogates the resistin-dependent down regulation of AdipoR1 and APPL1 and totally restored adiponectin-dependent phosphorylation of AKT. Collectively, these results indicate that resistin-dependent activation of TLR4 promotes the down regulation of APPL1 and adiponectin receptors leading to the alteration of adiponectin signalling. This could contribute, at least in part, to the impairment of the insulin-sensitizing effect of adiponectin at the neuronal level.

Disclosure

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OC10.2

Ondottella aurita-enriched high-fat diet prevents high-fat diet-induced insulin resistance

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Nuclear corepressor 1 (NCoR) associates with nuclear receptors and other transcription factors leading to transcriptional repression. Genetic studies have shown the presence of inactivating mutations of the NCoR gene in human tumours and we have found that NCoR depletion with siRNA in hepatocarcinoma SK-hep1 cells enhances invasion, tumour growth and metastasis in nude mice, while expression of the thyroid hormone receptor β (TRβ) increases NCoR levels, repressing tumorigenesis. We have now analysed human hepatocarcinomas, finding that NCoR expression is significantly downregulated and that there is a good correlation with TRβ in the tumours, indicating the relevance of these observations in the patients. Importantly, the use of siNCoR or the thyroid hormone receptor agonist 13C10.4

A genome-wide shRNA screen to identify genes regulating ERα signalling and oestrogen-dependent proliferation in breast cancer cells

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Over 70% of breast tumours express oestrogen receptor alpha (ERα). Stimulation with oestriol results in receptor binding to oestrogen response elements (ERE) and activates novel TR ligands capable of disrupting TGFβ/SMAD activity could constitute a novel therapeutic approach to block the progression of fibrotic diseases.

Reference

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Disclosure

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Oc11.2

serum glycine-4 levels and its association with cardiovascular risk predictor in women with polycystic ovary syndrome and healthy controls—pilot study

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Glycine-4 (Gpc-4) is novel adipokine interact with insulin receptor and affects insulin sensitivity in proteoglycans. Gpc-4 serum levels show gender differences; females having higher levels than men, what can suggest mediation by sex hormones. We investigated serum Gpc-4 levels and its association with cardiovascular risk predictors in women (20–35 years old) with PCOS (n=62) and healthy control (n=43) presented different sex hormones profile. The following CVD risk predictors: BMI, waist circumference (WC), total fat (TF), androoidal fat deposit (AFD), gynoidal fat deposit (GFD), AFD/GFD ratio (A/G), fasting serum glucose, insulin, HOMA, serum triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol and hormonal profile LH, testosterone, androstenedione (Adione), SHBG, Free Androgens Index (FAI) were estimated. Gpc-4 was determined by commercial ELISA kit. Serum Gpc-4 levels in women with PCOS was statistically significant higher than in control group (2.61 ± 1.17 vs. 1.55 ± 0.47 ng/ml). Serum Gpc-concentration positively correlated with BMI in both groups (P < 0.001), but with WC (P < 0.001), WHR (P = 0.005), TF (P < 0.001), AFD (P < 0.001), GFD (P = 0.008), A/G (P = 0.002) only in PCOS group. Serum Gpc-4 concentration were correlated positively with fasting serum insulin and HOMA in PCOS women and in control group (for both and in each group P < 0.001). We showed that Gpc-4 concentration positively statistically significant correlated with serum Adione and FAI levels in control group and we obtained only the tendency in PCOS group (P = 0.054) also with serum LH (P = 0.071). This original observation give new light on the role of Gpc-4 in women health, but because of some limitations further study is required.

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Oc11.3

miRNA profiling of H295R cells following stimulation of aldosterone production: a bioinformatic study

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Inappropriately high secretion of aldosterone can lead to hypertension and its various cardiovascular consequences. We previously showed that microRNA (miRNA) plays a significant role in the regulation of aldosterone biosynthesis. In this study we measured miRNA levels in H295R cells, the most commonly-used human adrenocortical cell line, and investigated how these change in response to the stimulation of aldosterone biosynthesis. H295R cells (n = 3 per group) were stimulated with either 100 nM angiotensin II (AngII), 10 mM dibutyl cyclic AMP (dbcAMP, to simulate ACTH effects) or 20 mM potassium chloride (KCl) for 24 h. Each treatment significantly increased aldosterone synthase (CYP11B2) mRNA relative to basal unstimulated cells. Microarray analysis also revealed significant and consistent changes in the quantities of specific miRNAs relative to basal levels: 20 miRNAs were differentially expressed in the AngII-treated cells, 68 in the dbcAMP-treated cells and 66 in the KCl-treated cells. Expression of 6 miRNAs was consistently altered across all three treatments, with the majority localising to one of two miRNA clusters located on either chromosome 13 or the X chromosome. Bioinformatic analysis with Ingenuity Pathway Analysis (IPA) software was used to predict miRNA targets for these six differentially-expressed miRNAs, but no direct effects on steroidogenic enzymes were identified. However, effects on various cholesterol-related genes, such as LDLR and ABCA1, were predicted. In conclusion, we have shown that consistent changes in miRNA profile result from various aldosterone-stimulating treatments in vitro. This includes a reduction in clustered miRNAs predicted to affect genes regulating cell cholesterol levels. This suggests a mechanism by which steroid biosynthesis could be affected and complements our results from aldosterone-producing adenoma (APA) tissue, which had consistent differences in mRNA profile relative to normal adrenal tissue. We now intend to investigate the impact of these miRNAs on cholesterol-related genes and corticosteroid biosynthesis.

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Oc11.1

central resistin infusion impairs FGFR2/FGFR3α-Klotho hypothalamic expression and promotes peripheral FGFR2 resistance: involvement of resistin/TLR4 signalling pathway

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FGF21 has recently emerged as a major regulator of metabolism and energy utilisation. FGF21 administration confers multiple metabolic benefits on insulin sensitivity, blood glucose, lipid profile and body weight in rodents and primates. FGF21 acts through a receptor complex consisting of FGF receptors (FGFR 1, 2, 3 or 4) and a co-receptor (Klotho (KLB), crucially required for FGF21 signaling. Although FGFRs are widely expressed, KLB is predominantly expressed in adipose tissue, liver, and hypothalamus making these as primary sites of FGF21 action. In obesity, circulating levels of FGFR2 are elevated, and the expected beneficial effects of endogenous FGF21 are impaired suggesting an FGFR2 resistance state. However, the precise pathways whereby obesity induces FGFR2 resistance remain unknown. In this study, we aim to investigate whether central resistin/TLR4 pathways could contribute to FGFR2 resistance. To test this hypothesis, we assessed, in C57BL6 mice and Wistar rats, the impact of IVC resistin infusion on the expression of FGFR2 and its receptor components in the hypothalamus and key peripheral insulin target tissues. Here we show that IVC resistin significantly decreased hypothalamic FGF21 expression in both mice and rats. Interestingly, the expression of FGFR1, the most abundant receptor in the hypothalamus, and KLB were also markedly reduced. Similar results were obtained in resistin treated SH-SY5Y neuronal cells. In rat peripheral tissue, IVC resistin increases the expression of FGFR2 in both liver and WAT, and markedly reduced WAT expression of FGFR1 and KLB. Importantly, the knockdown of TLR-4 in 4-SH-SY5Y cells almost completely abolished resistin-dependent down regulation of FGFR1 and KLB. Collectively, these findings indicates that central resistin, by a way of TLR4, down-regulates FGFR1, FGFR3 and KLB in the hypothalamus and promotes peripheral FGFR2 resistance as mirrored by the overexpression of FGFR2 in the liver and WAT and the down-regulation of FGFR1 in the muscle and WAT.

Disclosure
This work was supported by funds from University Paris Sud and CNRS (centre national de la recherche scientifique).

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Oc11.0

miRNA profiling of H295R cells following stimulation of aldosterone production: a bioinformatic study

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Inappropriately high secretion of aldosterone can lead to hypertension and its various cardiovascular consequences. We previously showed that microRNA (miRNA) plays a significant role in the regulation of aldosterone biosynthesis. In this study we measured miRNA levels in H295R cells, the most commonly-used human adrenocortical cell line, and investigated how these change in response to the stimulation of aldosterone biosynthesis. H295R cells (n = 3 per group) were stimulated with either 100 nM angiotensin II (AngII), 10 mM dibutyl cyclic AMP (dbcAMP, to simulate ACTH effects) or 20 mM potassium chloride (KCl) for 24 h. Each treatment significantly increased aldosterone synthase (CYP11B2) mRNA relative to basal unstimulated cells. Microarray analysis also revealed significant and consistent changes in the quantities of specific miRNAs relative to basal levels: 20 miRNAs were differentially expressed in the AngII-treated cells, 68 in the dbcAMP-treated cells and 66 in the KCl-treated cells. Expression of 6 miRNAs was consistently altered across all three treatments, with the majority localising to one of two miRNA clusters located on either chromosome 13 or the X chromosome. Bioinformatic analysis with Ingenuity Pathway Analysis (IPA) software was used to predict miRNA targets for these six differentially-expressed miRNAs, but no direct effects on steroidogenic enzymes were identified. However, effects on various cholesterol-related genes, such as LDLR and ABCA1, were predicted. In conclusion, we have shown that consistent changes in miRNA profile result from various aldosterone-stimulating treatments in vitro. This includes a reduction in clustered miRNAs predicted to affect genes regulating cell cholesterol levels. This suggests a mechanism by which steroid biosynthesis could be affected and complements our results from aldosterone-producing adrenoma (APA) tissue, which had consistent differences in mRNA profile relative to normal adrenal tissue. We now intend to investigate the impact of these miRNAs on cholesterol-related genes and corticosteroid biosynthesis.

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OC1.14

Uncacylated ghrelin and its analogue AZP-531 suppress ghrelin induced fat accumulation and feeding behaviours in high-fat diet fed male rats

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The peptides acylated and uncacylated ghrelin (AG and UAG) are produced predominantly in the stomach. AG is the only known circulating orexigenic hormone with obesogenic and insulin-desensitising properties. Recent evidence suggests that UAG can inhibit these activities of AG. To investigate potential inhibitory effects of UAG and AZP-531, a UAG analogue, on AG-induced appetite and obesity we used an established rat model of diet induced obesity. Animals were fed a high-fat diet, then at 3 weeks implanted with osmotic mini-pumps containing either vehicle, AG, UAG, AG + UAG, AZP-531 or AG + AZP-531 (n = 8 per group). All peptides were infused at 4 nmol/kg per h for 4 weeks. From 1 week before the start of infusion body weight and food intake were measured daily, blood sampling and assessments of feeding behaviour were made weekly. At the end of the experiment fat mass of different tissues, and body water and lean mass were measured. Tissues were also processed for mRNA analysis. The AG treated groups showed increased weight gain relative to the non-AG treated groups, but there was no significant effect of the UAG analogues. AG significantly increased total fat, but not lean or water mass. Remarkably, UAG and AZP-531 blocked AG-induced total fat accumulation, their inhibitory effects being localised to subcutaneous and retroperitoneal depots. UAG and AZP-531 also significantly suppressed AG-driven total food intake as well as aspects of AG-driven feeding behaviour, particularly speed of food intake. These activities may occur via a central mechanism since UAG and AZP-531 prevented the suppression of hypothalamic Mc-4r mRNA by AG. In conclusion, UAG analogues suppress AG-induced fat accumulation and feeding behaviours, and may therefore have therapeutic potential in clinical indications where hyperphagia and altered behaviour towards food are related to high ghrelin levels such as Prader-Willi syndrome.

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OC1.15

Preliminary analysis of the PRIMAVERA Study: reduxine safety in patients with alimentary obesity

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Background

The SCOUT trial showed that sibutramine produced weight loss with some increased cardiovascular morbidity but not mortality. But these results should not be extrapolated to a routine practice as a lot of the SCOUT participants had contraindications for sibutramine. In order to summarise data on efficacy and safety of sibutramine administration in routine clinical practice according to approved indications and to implement risks monitoring system in Russia, PRIMAVERA non-interventional study has been initiated (NCT01773733, clinicaltrial.gov).

Methods

98,774 obese patients from 142 Russian cities, treated with sibutramine 10–15 mg/day. Preliminary results were analyzed for 16,515 patients (82% – women, 18% – men). Patients were treated under control of body weight, blood pressure and pulse rate.

Results

2.5% of patients dropped out during screening phase due to contraindications to sibutramine use. 3% of patients stayed on treatment for 3 month, 65% – for 6 month and 29.5% – for 12 month. Mean weight loss was significant: 7.5 ± 2.8 kg by month 3, 14.3 ± 5.9 kg by month 6 and 18.8 ± 2.8 kg by month 12 (P < 0.01). Mean waist circumference decreased significant: 5.8 ± 3.1 cm, 10.7 ± 4.8 cm and 15.1 ± 5.9 cm by month 3, 6 and 12 respectively (P < 0.01). According to the Well-Being Questionnaire, body weight loss was accompanied by general increase in quality of life. Treatment with sibutramine was not associated with significant increase of blood pressure and pulse rate. Adverse events were reported for 2.8% patients. There were no reports of The Serious Adverse Events related to sibutramine use.

Conclusion

Based on preliminary analysis, sibutramine use according to approved indications is safe and effective for long-term treatment of obesity. Due to PRIMAVERA program the principles of sibutramine efficacy and safety monitoring are being implemented into routine clinical practice.

Disclosure

The research was supported by ‘Promomed RUS’ pharmaceutical company.

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Pituitary - Clinical

OC12.1

The Irish TSHoma study: a multicentre retrospective study

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TSH-secreting pituitary adenomas (TSHomas) are rare. Previously, the reported prevalence was one case per million populations although this is probably an underestimate. A recently published study reported a prevalence of TSHomas in Sweden of 2.8/million inhabitants.

Methods/design

Observational study conducted in four tertiary referral centres in Ireland. We retrospectively collected data on the prevalence, demographics, hormonal profile, tumour characteristics, and treatment outcomes for patients with TSHomas.

Results

21 patients (eight males) were diagnosed with TSHoma between 1968 and 2014. Mean age at diagnosis was 46 years. The prevalence of TSHomas in Ireland (Republic of Ireland and Northern Ireland) is 3.3/million inhabitants. This may be an underestimate as other centres may have TSHomas that were not included. At diagnosis, the median free thyroxine was 49.9% (IQR 50.3%) above the upper reference range. Eleven patients (52%) had TSH within normal range at diagnosis. 5/21 (23.8%) patients co-secreted GH and 4/21 (19%) patients had elevated prolactin. The median adenoma size was 13.5 mm (IQR 18.7) and 12/21 patients had a macroadenoma.15/21 patients were treated with surgery (two required craniectomy) as a primary therapy, 6/21 were treated with a somatostatin receptor ligand (SRL), five as a primary therapy. Somatostatin analogues normalised thyroid function in 4/5 patients. 8/21 patients underwent radiotherapy for either persistent active disease or tumour growth. 4/21 had hormonally active disease at the last follow up; three of these were treated with transphenoidal surgery and radiotherapy and one with SRL. 11/21 (52%) had other pituitary hormones deficiencies at the most recent follow up.

Conclusion

The prevalence of TSHoma in Ireland exceeds the previously cited estimate of one case per million. Multimodal treatment is often required to normalise thyroid function and prevent tumour growth.

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OC12.2

The ubiquitin-specific protease 8 gene is frequently mutated in adenomas causing Cushings’ disease

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Increased secretion of GH results in gigantism in children/adolescents and in acromegaly and gigantism are still unclear. To analyse the genetic causes and inherited/familial features in patients with pituitary gigantism, we studied a large international cohort. Genetic or inherited characteristics were observed in 39% of patients and included familial isolated pituitary adenomas (FIPA; n = 28), McCune–Albright syndrome (n = 7), Carney complex (n = 2), and MEN1 (n = 1).

Germline mutations in the AIP gene were found in 31% of tested cases; a microduplication at Xq26.3 was detected in two kindreds and ten sporadic patients with a novel polymorphic onset gigantism syndrome, termed X-linked acrogigantism (X-LAG). AIPmut positive patients were almost all males (95%), whereas X-linked acrogigantism group (X-LAG) consisted mostly of females (71%). AIPmut positive and X-LAG patients had significantly younger ages at first symptoms (13.5 and 1.5 years) and at diagnosis (16.8 and 3 years) than AIP negative patients (15 and 24 years respectively). Among non-X-LAG patients none had grown excessively before the age of 5 years. Pituitary lesions were usually macroadenomas and their size was not different in AIPmut, AIPwt, and X-LAG groups. All patients had marked hypersecretion of GH/GF1.

Prolactin co-secretion was more frequent in X-LAG than in AIPmut cases.

Conclusions

Syndromic or genetic features occurred in more than one third of patients with gigantism. Clinical presentation is affected by genetic pituitary adenomas and AIP mutations are common. X-LAG syndrome explained most of cases with childhood gigantism.

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OC12.4

The changing faces of corticotroph-cell adenomas: the role of proconvertase 1/3

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The changing faces of corticotroph-cell adenomas: the role of proconvertase 1/3

Introduction

The possible change in the pattern of hormonal secretion by pituitary tumours is a very intriguing issue indeed, notably in the case of corticotroph-cell adenomas.

Methods/design

We retrospectively reviewed the records of 1259 consecutive endoscopic endonasal surgical procedures for pituitary adenomas from 1998 to 2013. Of these, 132 were ACTH-secreting adenomas associated with Cushing’s disease (CD) and 44 were silent corticotroph-cell adenomas (SCA). During the follow-up, seven patients (four men and three women) showed a transformation of their clinical expression from SCA to CD or, more rarely, vice versa. Of these, to date only three patients with corticotroph-cell adenomas changing their pattern of hormonal secretion during the follow-up were re-operated. Then, we examined the expression of proconvertase 1/3 (PC1/3), which plays an important role in the POMC processing within the pituitary, in tissue specimens obtained from these three patients with SCA that had developed clinical and laboratory features of CD at the time of recurrence, using both immunohistochemistry and quantitative real time-PCR.

Results

The data indicated that the immunohistochemical PC1/3 expression was negative or weak and focally positive in tissue specimens obtained in the three patients at the time of first operation (SCA), whereas we observed a strong expression in the majority of the neoplastic cells in the same three patients at the time of recurrence, when they had become CD. The PC1/3 expression, as evaluated using immunohistochemistry, showed a significant correlation with the PC1/3 levels obtained by qRT-PCR in assessing the increase of PC1/3 expression from SCA to CD. Twelve cases of SCA without changing their phenotype during the follow-up were used as controls: both the immunohistochemical PC1/3 expression and level of PC1/3 obtained by qRT-PCR were absent or weak in scattered neoplastic cells.

Conclusion

This study provides insight into the crucial role of the PC1/3 in the mechanism(s) of transformation of phenotype from SCA to CD.

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OC12.3

The genetic causes of pituitary gigantism

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Increased secretion of GH results in gigantism in children/adolescents and in acromegaly in adults; the relative roles of the various genetic causes of
The clinical characteristics of X-linked acro-gigantism syndrome

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X-linked acro-gigantism (X-LAG) is a rare novel genomic syndrome of pituitary gigantism that has a typical onset within the first year of life in children of normal or even low birth weight. X-LAG patients have microduplications on chromosome Xq26.3 that includes a gene GPR101, which is highly upregulated in pituitary tumor tissue of affected patients. We performed a study of all 18 known X-LAG syndrome patients currently in the NICHD-University of Liège database to describe the clinical phenotype and therapy responses. All 13 sporadic cases had unique duplications; the inheritance pattern in familial cases was X-linked dominant. Typically, the abnormal growth was noted within the first year of life but could begin in the initial months of infancy. Despite significant somatic overgrowth (≥ 4 SDS height/weight), diagnoses of pituitary macroadenoma/hyperplasia were not made until usually > 2 years after excessive growth began. A number of familiar acromegaly signs/symptoms accompanied somatic overgrowth, including acral enlargement and facial changes (including widely spaced teeth in some cases). About 25% of cases had increased appetite, and signs of insulin resistance (e.g. acanthosis nigricans) were reported. At diagnosis, patients had extremely elevated GH and IGF1 levels, which were accompanied by variably severe hyperprolactinemia. Control of growth was difficult to achieve in many cases, particularly those where primary neurosurgery did not fully resect the involved tissue. Efficacy of traditional somatostatin analogs was notably poor, whereas adjuvant pegvisomant therapy did provide control of IGF1 and slowed growth. However, due to the need for aggressive therapy to arrest excessive growth, postoperative hypopituitarism was frequent. The mechanisms behind the excessive stimulation of pituitary growth and elevated hormonal output are being studied, but both pituitary and hypothalamic aetiologies are possible, for example, due to high levels of GHRH receptor staining in pituitary tumors in the face of normal or elevated circulating GHRH in some patients.

Disclosure

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Guided Posters
Adrenal insufficiency (AI) requires life-long glucocorticoid (GC) treatment, which is associated with an increased risk of metabolic syndrome (MS), probably due to cortisol overexposure for multiple drug daily doses, together with an impairment of quality of life (QoL). Moreover treatment compliance (TC) is reported to be suboptimal in AI patients. The current study aimed at investigating the impact of the switch from twice/thrice daily conventional GCs to once daily dual-release-hydrocortisone (DR-HC) treatment on metabolic profile, QoL and TC in patients with primary AI (PAI) and secondary AI (SAI). Thirty-five patients (12 with PAI; 19 with SAI; 7F, 22M, 20–77 years), 17 treated with cortisone acetate (37.5–75 mg/day) and four with cortisone acetate (30–50 mg/day) and 25 patients with SAI (9F, 14M, 20–77 years), 15 treated with cortisone acetate (17.5–87.5 mg/day) and eight with HC (15–20 mg/day) entered the study and were evaluated before and 6 months after the switch to DR-HC (PAI: 20–60 mg/day and SAI: 20–40 mg/day).

At 6-month-follow-up, in PAI patients, body weight (BW) (P = 0.017), BMI (P = 0.003), WC (P = 0.007) and WHR (P = 0.036) significantly improved and a trend to a significant improvement was also found for waist circumference (WC) (P = 0.086). A diagnosis of MS, performed in two patients (17%) at baseline, was not confirmed after 6 months. In SAI patients, BW (P = 0.001), BMI (P = 0.003), and WC (P = 0.007) significantly improved. A clear diagnosis of MS, performed in seven patients (30%) at baseline, was confirmed only in 4 (17%) of these patients after 6 months. In a subgroup of 12 patients with AI, visceral adiposity index (VAI), an indicator of adipose function and metabolism, which seems to indirectly express the cardiometabolic risk, significantly improved (P = 0.05) while an improvement in insulin sensitivity index (ISI 120) (P = 0.052) was reported 120 min after glucose load. In the subgroup of ten patients considered for the change to DR-HC in patients with AI improved BW, BMI, WC, prevalence of MS, glucose tolerance and insulin sensitivity, QoL and TC.

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elective surgery with general anaesthesia (617, 269–1379), combat stress (441, 69–789), acute trauma (235, 23–1257), and healthy controls (197, 67–752 nmol/l).

Initial peak concentrations after HC exceeded stress levels, but serum cortisol decreased to under the median of controls several hours before repeat administration of oral, i.v., and i.m. bolus. By contrast, HC IV-C maintained steady state cortisol levels above the median of stressed controls throughout. Linear pharmacokinetic modelling combined with mixed effects regression calculated the optimal dose and administration mode as an initial bolus of 50–100 mg HC i.v., followed by continuous i.v. infusion of 200 mg/24 h. Continuous i.v. rather than bolus administration of HC will avoid dangerous intermittent trough levels and thus represents the recommended administration mode for patients with adrenal insufficiency exposed to pathologic stress due to trauma, sepsis, or surgery.

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Incidence of adrenal insufficiency and its relation to mortality in patients with septic shock

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Background

The hypothalamic–pituitary–adrenal axis has a pivotal role in combating acute insults. Glucocorticoids play a role directly or indirectly in the maintenance of normal vascular tone and in potentiating the vasconstrictor action of catecholamine, associated with septic shock.

Aims

To determine the incidence of adrenal insufficiency (AI) and its relation to mortality in patients with septic shock.

Methods and materials

In patients of septic shock, APACHE II score was calculated and serum cortisol was measured at the time of admission and 1 h after giving 250 mg ACTH. Hydrocortisone was added to inotropics in all patients after drawing second blood sample for serum cortisol and was continued till 7 days or less. In our study, the patients with inadequate adrenal response were divided into two groups: i) absolute AI – baseline cortisol <20 μg/dl and increment ≤9 μg/dl after the ACTH stimulation test and ii) relative AI – patients with baseline cortisol ≥20 μg/dl and increment <9 μg/dl. Statistical analysis used: data were analysed with SPSS version 17 and were presented in the values of mean, median, and percentages. The P value of <0.05 was considered significant.

Results

The incidence of AI in septic shock was (n=100) was 42% (in absolute 14% and relative 28%). The incidence of AI in septic shock was 42% (absolute 14% and relative 28%). The mortality rate was 48%, and it was higher in patients with AI than in patients without AI (P=0.017). The APACHE II score >25 carried higher mortality rate than a score of <25 (P<0.001). Baseline serum cortisol >45 μg/dl had exceptionally high likelihood of mortality (OR 50, P<0.001). Among those who survived, inotropic support was required for longer period in relative as compared with absolute AI and to non-AI.

Conclusions

AI is prevalent among patients with septic shock. We found that higher APACHE II scores were associated with higher rates of adrenal failure and mortality in patients with septic shock. There also appears to be a bimodal distribution of mortality with adrenal status in patients with septic shock.

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Mild cognitive deficits in patients on long-term, stable hydrocortisone replacement for primary adrenal insufficiency: a case–control study

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Background

Hydrocortisone replacement for primary adrenal insufficiency (PAI) is targeted to mimic circadian endogenous cortisol secretion. Nevertheless, patients on stable replacement do not appear to have cognitive impairments.

Aims

We aimed to investigate the impact of PAI on cognitive performance compared to healthy controls.

Methods

We performed a case–control study with 23 patients who were in stable replacement for at least 3 months and 23 healthy controls matched for age, sex, and education. The Edinburgh Inventory of Cognitive Functions and a computer-based attention test were used to evaluate cognitive performance.

Results

Patients in stable PAI showed trends towards lower scores in the Edinburgh Inventory for three of the seven domains (attention, memory, and planning and organisation) but did not reach significance. In the computer-based attention test, patients in stable PAI showed slower reaction times but no difference in accuracy.

Conclusions

Mild cognitive deficits in PAI are not present and thus do not indicate an increased risk for dementia.

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Autoimmune polyendocrine syndrome in India: clinical aspects, AIRE mutations, and functional analysis

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Introduction
Autoimmune polyendocrine syndrome 1 (APS1) is an uncommon, serious autosomal recessive disorder, due to AIRE gene mutations which result in impaired central tolerance. India has a complex genetic structure and also communities with high prevalence of consanguinity, which may result in varied clinical manifestations and genetic mutations.

Aims
To study clinical features, interferon-γ antibodies (IFNA), AIRE mutations, and in-silico functional analysis of novel mutations in Indian patients with APS1.

Patients and methods
Twenty patients (17 families) with clinical features of APS1 were studied. Twelve patients previously reported by us (Clin Genet 2009 76:441) were included in analysis. Clinical features (including mortality on follow-up), IFNA, bidirectional sequencing of AIRE gene, and in-silico functional analysis of novel AIRE mutations were studied.

Results
Patients had three (n=9), two (n=9), or a single (n=2, family members) major manifestation of APS1, in addition to various other organ-specific autoimmune disorders. On follow-up, mortality was high (n=6, 30%), occurring at early age (3-5 years). IFNA was elevated with high titres in all patients, but within normal range in family members with heterozygous mutations/WT sequence. Ten different mutations were detected, with C322fsX372 being most frequent (six families). Novel mutations included p.V80G (n=3), in three different families from an in-bred community in Kerala, South India), p.L11P, p.C302X, and p.X546L+59a (c.1637G>T; terminal codon). The Finn-major mutation, R257X, was present in one patient. No specific genotype-phenotype correlation was observed. Functional analysis of two novel missense mutations (V80G and L11P) in the CARD domain revealed increased instability resulting from changes in intra-helical hydrogen binding.

Conclusions
Indian patients with APS1 syndrome had high mortality. IFNA was an inexpensive and sensitive marker for APS1. Multiple different AIRE mutations were present, including four novel mutations. Functional analysis of novel mutations revealed disruption of intra-helical hydrogen binding and increased instability.

Disclosure
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Steroid profiling by liquid chromatography–tandem mass spectrometry in patients with non-secreting adrenocortical adenomas and subclinical hypercortisolism

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Steroid profiling by liquid chromatography–tandem mass spectrometry (LC–MS/MS) offers an accurate and simultaneous detection of a panel of steroids with several advantages over traditional assays. However, only a few studies have investigated the steroid profiling in sporadic adrenocortical adenomas. Our aim was therefore to investigate steroid secretion by LC–MS/MS in patients with non-secreting adrenocortical adenomas (NSA) and subclinical hypercortisolism (SH), by analysing cortisol, 21-deoxycortisol (21-DF), 11-deoxycortisol, 17-hydroxyprogesterone (17-OHP), androstenedione, DHEA, testosterone, progesterone, 21-deoxycorticosterone (DOC), and corticosterone. Steroids were evaluated in basal condition and 60 min after stimulation with 250 μg of 1,24 ACTH. Patients (n=94) were analysed at baseline and compared to 190 sex- and age-matched controls. DHEA levels were progressively decreased in NSA and SH, respect to controls. Androstenedione and testosterone levels were also reduced in females. A significant positive correlation between basal DHEA and ACTH was found (correlation coefficient 0.403, P<0.001), supporting the hypothesis that decreased stimulation of contralateral cortex by reduced ACTH levels is the likely cause of DHEA reduction. Considering the known anti-glucocorticoid effects of DHEA in adipocytes, we tested the potential effects of reduced DHEA on metabolic alterations. Increased BMI (correlation coefficient 2.01, P<0.001) and cortisol after dexamethasone test (correlation coefficient 0.14, P<0.001), and reduced DHEA (correlation coefficient −5.70, P<0.034), were all factors independently associated with the increase of waist circumference. Stimulation study was performed on 56 patients and revealed that subjects with SH had higher levels of cortisol, 21-DF, DOC, corticosterone, and lower levels of DHEA and androstenedione respect to NSA. Steroid profiling by LC–MS/MS highlighted important clues into the secreting pattern of adrenocortical adenomas. Further studies are needed to address the clinical implication of the increased levels of gluco- and mineralocorticoid precursors in the pathogenesis of cardiovascular and metabolic correlates in SH.

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Urinary glucocorticoid metabolites and adrenal incidentalomas?
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Objective
Urinary cortisol and metabolites represents total cortisol production and metabolism. We assessed these metabolites to compared the information that could be extracted compared to the one provided by a sole cortisol assay.

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Design and patients

An inexpensive multiplex mass spectrometry assay was set up to quantify cortisol and its metabolites in 43 patients with benign secreting (AT+) or silent (AT-) adrenal tumours compared to 48 lean (NI) or 143 obese (Ob) subjects, and to 26 patients with a Cushing’s disease (CD). Their routine initial investigation included immunoreactive quantification of urinary free cortisol (UFC).

Results

Cortisol and metabolites were over-excreted in CD but not in Ob subjects. NI and Ob were thus pooled in a control population (Cl). Cortisol, tetrahydrocortisol (THF), and tetrahydrocortisone (THE) excretions were significantly increased in AT compared to Cl subjects whereas immunoreactive UFC was similar. A logistic regression retaining cortisol, THF, and cortisol or metabolites a logistic regression retaining cortisol, alloTHF, and n- and b-cortolone as significant analytes allowed the construction of a receiver-operating characteristics (ROC) curve significantly better than the curve generated by cortisol alone (area under the curve (AUC) 0.927 vs 0.729, respectively, P < 0.0001). More importantly, although there was no significant difference between Cl vs AT subjects for cortisol or metabolites a logistic regression retaining cortisol, alloTHF, and n- and b-cortolone as significant analytes generated a ROC curve performing significantly better than cortisol alone (AUC 0.910 vs 0.635, respectively, P < 0.0001).

Conclusion

Cortisol and metabolites excretion is modified in AT, including AT-, patients even without modification of UFC. Clinical usefulness of these biomarkers has to be investigated in prospective studies following-up patients with AT.

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**GP 02.03**

Differential expression of the PKA subunits in adrenocortical adenomas

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Recently, mutations in the PRKACA (catalytic subunit n of the PKA) gene have been identified as causative in 35% of adrenocortical adenomas (ACA) with overt Cushing’s syndrome (Beuschlein et al. 2014). These mutations lead to constitutive activation of PKA signaling and subsequently to an excessive production of cortisol. Protein kinase A is a heterotrimer consisting of two catalytic and two regulatory subunits with several isoforms (Cα, β, γ, RIIα, RIIβ, and RIIγ). The stable tetramer is inactive, only upon cAMP induced dissociation of the regulatory subunits the active catalytic subunits are released. Here, we investigated the expression of the different PKA subunits in a large set of adrenal tumors. We performed immunohistochemistry staining of all PKA regulatory subunits and Cα on FFPE tissue from normal adrenal glands (n = 8), ACA (n = 65, 30 cortisol-producing/CPA, 17 aldosterone-producing, and 18 inactive) and adrenocortical carcinomas (ACC; n = 29, seven cortisol-, three androgen-, 12 mixed hormone-producing, and seven inactive). Our results indicate a significantly decreased expression of RIIβ in CPAs, but only in the PRKACA mutated samples. A tendency for reduced expression under PRKACA mutation was also observed for RIIα. No change in expression was found for the other two regulatory subunits or Cα. While reduced RIIβ expression in CPAs had previously been described (Mantovani et al. 2008), until now, this phenomena could not be linked to PRKACA mutational status. The former hypothesis that the decreased level of RIIβ leads by itself to the cortisol excess seems to be wrong, because RIIβ was not significantly changed in both ACA and ACC from patients with overt Cushing’s syndrome but without PRKACA mutation. We therefore postulate that the reduced protein expression of RIIβ in CPA described earlier is a direct or indirect consequence of the newly identified mutation and not a general feature in CPAs. If this decrease arises post-transcriptionally or at transcriptional levels still needs to be elucidated.

Disclosure

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**GP 02.04**

Mortality in patients with incidentally discovered adrenocortical adenomas: the experience of San Luigi Hospital

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Background

Adrenal incidentalomas are found in 3–7% of radiological series and many of them are adrenocortical adenomas. Autonomous cortisol secretion without clinical signs of overt hypercortisolism is a common finding in these patients. Studies reported metabolic derangement and increased cardiovascular risk associated with this state of subtle cortisol excess, however scanty data are available on the natural history of this condition.

Aim

To assess the rate of mortality in patients with incidentally discovered adenomas.

Methods

We studied 110 patients (39 males and 71 females) with incidentally discovered adrenocortical adenomas from 1998 to 2013. Metabolic and hormonal parameters were determined. We collected the following data: blood pressure, plasma glucose, lipid profile, cortisol levels after 1 mg dexamethasone suppression test (1 mg-DST), plasma ACTH, and urinary free cortisol. Mortality data were obtained from the demographic registers.

Results

Mean age of patients was 67 years, with a mean follow-up of 94 months. Fourteen (12.7%) patients died: 4 (28.6%) for cancer, 7 (50.0%) for cardiovascular, and 3 (21.4%) for respiratory/infective causes. Twelve of them (85.6%) had 1 mg-DST > 1.8 μg/dl (four had hypertension, four dyslipidaemia, and four diabetes) while 54/86 patients alive at the last follow-up (60.2%) had 1 mg-DST > 1.8 μg/dl (P = 0.04). Survival probability was significantly reduced in patients with 1 mg-DST > 1.8 μg/dl, with a hazard ratio of death of 3.64 (95% CI, 1.34–9.7; P = 0.013). Age did not differ between patients alive or dead at the last follow-up (65.1 ± 9.8 years vs 65.1 ± 9.8 years, NS).

Conclusion

Patients with incidental adrenal adenomas and autonomous cortisol secretion heralded by cortisol after 1 mg-DST > 1.8 μg/dl may be at increased risk of mortality compared to patients with non-secreting adenomas. Excess mortality is mainly related to cardiovascular events.

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**GP 02.05**

Comparison between PET–CT and CT in the diagnosis of recurrence of adrenocortical carcinoma

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Adrenocortical carcinoma (ACC) is a rare tumour characterised by a high rate of recurrence following radical surgery. Surgery of recurrent ACC may increase survival; thus, it is mandatory a timely and accurate detection of recurrence, either to increase the chance of radical extirpation or to avoid unnecessary surgery. This study investigated the role of PET–CT in the diagnosis of recurrence of ACC during follow-up of disease-free patients and analysed whether this tool may improve the therapeutic strategy. A retrospective evaluation of the use of PET–CT was done in ACC patients with suspected recurrence at CT imaging during their follow-up. Data of 57 patients followed at our center were retrieved. Recurrence was confirmed by pathology when lesions were removed (23 cases), or fine-needle biopsy (five cases), or detection of unequivocal tumour progression during follow-up (29 cases). CT scan of the 57 patients showed a total of 153 lesions while PET–CT showed at least one focal uptake in 40 patients (70.2%) for a total of 99 lesions. For liver lesions, PET–CT showed at least one focal uptake in 40 patients (70.2%) for a total of 99 lesions. For liver lesions, PET–CT showed at least one focal uptake in 40 patients (70.2%) for a total of 99 lesions. For liver lesions, PET–CT showed at least one focal uptake in 40 patients (70.2%) for a total of 99 lesions.

Recurrence was confirmed by pathology when lesions were removed (23 cases), or fine-needle biopsy (five cases), or detection of unequivocal tumour progression during follow-up (29 cases). CT scan of the 57 patients showed a total of 153 lesions while PET–CT showed at least one focal uptake in 40 patients (70.2%) for a total of 99 lesions.

Recurrence was confirmed by pathology when lesions were removed (23 cases), or fine-needle biopsy (five cases), or detection of unequivocal tumour progression during follow-up (29 cases). CT scan of the 57 patients showed a total of 153 lesions while PET–CT showed at least one focal uptake in 40 patients (70.2%) for a total of 99 lesions.
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**GP.02.06**

DNA methylation of FKBP5 and its relationship with hippocampal volumes in Cushing’s syndrome patients

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Introduction

FKBP5 is a protein that regulates glucocorticoid receptor sensitivity, via an ultra-short negative feedback mechanism. Variations in the FKBP5 gene can influence the response to glucocorticoids (GC). Hypercortisolism plays a role on impairment of brain function and could be mediated by epigenetic variations of the FKBP5 gene. Cushing’s syndrome (CS), a disease characterized by hypercortisolism, is associated with memory deficits, lower hippocampal volumes and a wide range of cognitive impairments. Recently, it has been demonstrated that GC-induced methylation changes in FKBP5 observed in blood DNA can serve as a proxy to both methylation and expression changes in the brain. We aimed at evaluating DNA methylation of FKBP5 in blood and its relationship with memory and hippocampal volumes (HV) in CS patients.

Patients and methods

33 CS patients with memory impairments (nine active and 24 cured) and 33 matched healthy controls were included. Memory tests, 3Tesla MRI of the brain, and DNA extraction from total leukocytes was carried out in all subjects. DNA from CS patients and healthy controls were bisulfite treated, PCR amplified, and pyrosequenced to assess a total of 34 CpG dinucleotides in introns 1, 2, and 5 of the FKBP5 gene.

Results

We observed lower methylation in introns 2 and 5, in both cured and active CS patients compared to controls (P<0.001 and P<0.05 respectively). We also observed a positive correlation between the total methylation values and hippocampal volumes in active patients (r=0.86, P<0.01 left HV and r=0.80, P=0.01 right HV), but not with memory tests. However, there were multiple correlations between single CpG dinucleotides and memory test variables (P<0.01).

Conclusion

As lower DNA methylation in FKBP5 is associated with higher GC exposure and gene expression, our results demonstrate a relationship between blood DNA methylation and GC-induced brain impairments in CS patients.

Disclosure

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**GP.02.08**

ACTH-ectopic syndrome in four patients, caused by pheochromocytoma

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Phaeochromocytomas are responsible for the development ACTH-ectopic syndrome in 5% cases. Less than 1% phaeochromocytoma accompanied by symptoms of ACTH-dependent hypercortisolism. We observed four cases of ACTH-secreting pheochromocytoma during 2 years. All patients were women from 50 to 63 years. The disease duration ranged from 6 months to 5 years.

The clinical picture presented the signs of hypercortisolism (matronism, hyperpigmentation of the skin, the redistribution of fatty tissue on the central type, and steroid myopathy) and hypercorticotilamia (arterial hypertension, tachycardia, shortness of breath, and frequent urination). Hormonal blood study found: morning ACTH 43.0-189.0 pg/ml (normal 7.0-66.0) evening 179.8-291.0 (normal 0-30.0), morning cortisol 962-4655 nmol/l (normal 123.0-626.0), evening 1256-2460 (normal 46.0-270.0), free cortisol in 24 h urine 3726.0-3828.0 nmol/day (normal 60.0-413.0); metanephrine in daily urine in three of four patients (638.0-1481.0 g/day at the rate of 25.0-312.0 g/24 h). Conversely, the performance of UFE in mild CS was low (84.6% SE and 75% SP; cut-off value >88.7 μg/24 h). Conversely, the performance of UFF in mild CS was low (84.6% SE and 75% SP; cut-off value >44.2). UFF and UFE showed an optimal diagnostic performance with 100% SE and 100% SP in moderate to severe CS (UFF ≥2× ULN). The performance of urinary steroids was not different according to age, sex, disease aetiology, and disease status in CS.

Conclusions

UFF measured by LC–MS/MS seems to be a new and good biomarker in diagnosing CS especially in patients with mild hypercortisolism at higher risk for misdiagnosis with UFF.

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**GP.02.07**

Urinary free cortisol as a potential biomarker in diagnosing patients with mild Cushing’s syndrome

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Introduction

Urinary free cortisol (UFC) determination has suboptimal sensitivity (SE) and specificity (SP) especially in mild Cushing’s syndrome (CS).

Aim

To determine the performance of UFC and its metabolite cortisone (UFE) measured using accurate assays such as HPLC and LC–MS/MS in diagnosing patients with CS.

Patients and methods

Sixty-seven patients with CS were compared to 49 sex- and age-matched non-CS. UFC and UFE levels were assessed by HPLC until 2009 and afterwards by LC–MS/MS. The mean value of two 24-h urine collections was used for the analysis. SE and SP were calculated at different cut-off values using ROC curve analysis.

Results

UFF and UFE values were significantly higher in patients with CS. However, the diagnostic performance of UFF by HPLC was low with 75.8% SE and 81.1% SP (cut-off value >33.9 μg/24 h). The performance of UFF by LC–MS/MS was 88.2% SE and 91.2% SP (cut-off value >47.4 μg/24 h). The performance of UFE was better than UFF by both assays. UFE by LC–MS/MS showed 97.1% SE and 91.7% SP by using a cut-off value >88.7 μg/24 h. When CS patients were stratified according to disease severity, UFE by LC–MS/MS showed a good diagnostic profile also in mild CS (UFF <2× ULN) with 92.3% SE and 91.7% SP (cut-off value >88.7 μg/24 h). Conversely, the performance of UFF in mild CS was low (84.6% SE and 75% SP; cut-off value >44.2). UFF and UFE showed an optimal diagnostic performance with 100% SE and 100% SP in moderate to severe CS (UFF ≥2× ULN). The performance of urinary steroids was not different according to age, sex, disease aetiology, and disease status in CS.

Conclusions

UFF and UFE are markers of hypercortisolism and can be used in patients with mild CS. UFC and UFE showed an optimal diagnostic performance in patients with CS.

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**GP.03.01**

**Pregnancy in women with non-classical congenital adrenal hyperplasia: time to conceive and outcome**

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**Background**

Non-classical 21-hydroxylase deficiency (NC21OHD) is a mild form of congenital adrenal hyperplasia associated with different degrees of postnatal virilisation. Elevated serum androgen concentrations have been reported to be a risk factor for infertility, early pregnancy loss, and recurrent miscarriages in women with polycystic ovarian syndrome (PCOS).

**Aims**

The aim of this study was to assess time to conceive and pregnancy outcome in NC21OHD women in correlation with glucocorticoid (GC) therapy and androgen levels.

**Patients and methods**

We conducted a retrospective observational study in a tertiary medical centre. The outcome of 130 pregnancies among 59 women (mean age at diagnosis 20 ± 9.5 years and mean age at first pregnancy 29 ± 5 years) with biochemical and genetic diagnosis of NC21OHD was reviewed. Androgen and 17OHP levels were measured before and during each trimester. The mean GC dose was 7.4 ± 3.3 mg hydrocortisone/m2.

**Results**

There was no difference in time to conceive between pregnancies of women with and without treatment (7.7 ± 11 months vs 7.5 ± 25 months). There were 29 pregnancies without GC therapy and 101 with GC therapy. There was no significant difference between the rate of miscarriages between treated and untreated pregnancies (25% vs 17%, respectively, P = 0.6). Birth weight was significantly lower in GC-treated pregnancies compared to untreated pregnancies (2.9 ± 0.4 kg vs 3.2 ± 0.5 kg, respectively, P = 0.03). Androgen and 17OHP levels were similar in pregnancies that ended with miscarriage and those that ended with live birth.

**Conclusions**

Time to conceive is similar between treated and untreated pregnancies in NC21OHD women. In contrast to previous reports, there was no difference in miscarriage rates between treated and untreated pregnancies. There was significant decrease in birth weight in treated pregnancies despite the use of low doses of GC.

DOI: 10.1530/endoabs.37.GP.03.01

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**Table 1**

Correlations of Hb and Hct with androgens and 17-OHP in women.

<table>
<thead>
<tr>
<th>Androgens</th>
<th>17-OHP</th>
<th>Testosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>0.42</td>
<td>0.4129</td>
</tr>
<tr>
<td>Hct</td>
<td>0.3564</td>
<td>0.4346</td>
</tr>
</tbody>
</table>

There was a difference in Hb and Hct between patients with high, normal, and low androstenedione levels (ANOVA, P < 0.01). Hct, but not Hb, was significantly different with high, normal, and low testosterone levels (ANOVA, P < 0.01). *Post hoc* analysis showed mean Hb and Hct levels were significantly different between high and low androstenedione and testosterone subgroups (P = 0.001).

**Conclusions**

There is a positive correlation between adrenal androgens and erythropoiesis in women with CAH. This effect is significant not only at high levels of androgens but also at low levels. Suboptimal control of androgens in this group of patients may increase the risk of polycythemia and anaemia. Use of Hb and Hct as markers of disease control should be investigated in larger populations of CAH women.

DOI: 10.1530/endoabs.37.GP.03.02

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**GP.03.02**

**Androgens and erythropoiesis in females: an insight from patients with congenital adrenal hyperplasia**

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**Background**

Androgens promote erythropoiesis and have been used for the treatment of anaemia. Furthermore, polycythemia is a known side effect of androgen therapy. In congenital adrenal hyperplasia (CAH), elevated adrenal androgens cause virilisation of female patients. Glucocorticoid treatment reduces androgen levels but there is a difficult balance between excess androgens and suppressed androgens due to excess glucocorticoid treatment.

**Aim of study**

To investigate the relationship between androgens and erythropoiesis in females with CAH.

**Methodology**

A retrospective case note review of 63 patients with CAH. Androgen levels and blood counts performed on the same day were collected and analysed in 44 patients; patients with medical conditions known to affect erythropoiesis were excluded.

**Results**

44 patients were studied (27 females); mean age was 35.5 ± 13.2 years. In women, there was a positive correlation of testosterone, androstenedione and 17-OHP levels with haemoglobin (Hb) and haematocrit (Hct).

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**GP.03.03**

**Radiofrequency bipolar ablation therapy for primary aldosteronism patients: investigator-initiated exploratory clinical trial**

Kei Takase1, Kazumasa Seiji2, Ryo Morimoto2, Yoshizugu Ikawara2, Yoshikiyo Oos2, Kei Onata2, Masataka Kudo1, Tomo Kinoshita1, Fumitoshi Sato2 & Sadayoshi Ito2

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**Purpose**

To evaluate safety and efficacy of percutaneous radiofrequency ablation therapy for unilateral aldosterone producing adrenal adenoma in normalising aldosterone secretion.

**Patients**

Eight cases of aldosterone producing adrenal adenoma with following conditions: i) CT detectable adenoma without any risky organs on a puncture route. ii) Intervening adipose tissue between target adenoma and adjacent risky organs (pancreas or intestine). iii) Unilateral single functioning macroadenoma with aldosterone hypersecretion proven by adrenal venous sampling.

**Methods**

CT guided puncture of adrenal adenoma with one or two (accoring to the size of the adenoma) bipolar radiofrequency ablation needle was performed, followed by ablation with total power of 4-6 kJ. Blood pressure was monitored with an arterial catheter during the procedure. Aldosterone levels in serum and 24-h urine collection 7 days after ablation were evaluated as primary outcomes. ACTH, cortisol, serum aldosterone, renin activity, osmotic pressure, potassium level, urine osmolality, and antihypertensive medication dose at screening, 3, 7, 28, and 84 days after ablation therapy were also evaluated. Ablation effect was morphologically evaluated by enhanced CT 7 days after treatment.

**Results**

In all cases, aldosterone levels in serum and 24-h urine were significantly decreased; Serum potassium level was normalized without anti-aldosterone therapy. Postoperative CT showed complete ablation in six cases and subtle residual enhanced area in two cases. Doses of anti-hypertensive medication were reduced in all cases including two drug-free patients after ablation. No severe procedure-related complication was observed.

**Conclusion**

Bipolar radiofrequency ablation is thought to be safety and effective in treating primary aldosteronism.

**Disclosure**

Project of promoting innovative medical devices by Ministry of Health, Labour and Welfare, Japan.

DOI: 10.1530/endoabs.37.GP.03.03
Introduction
We report the largest case series of concomitant prolactinoma and aldosterone-producing adenoma (APA), diagnosed in four patients from the German Conn Registry and in three patients at the Hypertension Unit, University of Turin. A disproportionate number (five out of seven) presented with macro-prolactinomas indicating that elevated prolactin (PRL) concentrations may play a role in APA formation. Further, increased expression of PRLR in the zona glomerulosa could sensitise the adrenal gland to the high circulating levels of PRL in prolactinoma patients.

Methods
PRLR gene expression data was from the GTEx Portal database2 (dbGaP accession number phs000424.vN.pN; www.gtexportal.org). Transcriptional profiles of eight APA and three normal adrenals were compared using an Affymetrix GeneChip HG-U133 Plus 2.0 gene expression platform. Effects of PRL were tested on CYP11B2 gene expression levels and aldosterone production in NCI H295R cells.

Results
The uterus and the adrenal gland expressed the highest levels of the PRLR gene expression in APA compared to normal adrenals. In H295R cells PRL (100 nM) resulted in a 1.35 ± 0.02-fold upregulation in CYP11B2 gene expression and a 1.26 ± 0.07-fold increase in aldosterone production.

Conclusion
High levels of PRL result in CYP11B2 upregulation and an increase in aldosterone production in vitro and may play a role in APA development in cases of concomitant prolactinoma-APA.

DOI: 10.1530/endoabs.37.GP.03.04

GP03.05
Short-term blood pressure response to mineralocorticoid-receptor blockade in aldosteroneism: primary hyperaldosteronism vs aldosterone-associated hypertension/low-renin hypertension
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Introduction
Some authors consider aldosteronism to be a spectrum, ranging from aldosterone-associated (or low-renin) hypertension (AAH) to primary hyperaldosteronism (PHA) due to bilateral adrenal hyperplasia. Thus, blood pressure (BP) response to mineralocorticoid-receptor blocker (MRB) could be similar.

Methods
Retrospective analysis of 60 patients. Screening per Endocrine Society guidelines, positive screening: aldosterone (pg/ml) to direct-renin (pg/ml) (ARR) ≥ 25. 25-mg Captopril test (CAP) on doxazosine and/or long-acting verapamil, positive for PHA if aldosterone > 170 pg/ml or ARR > 50, 1 or 2 h post-captopril. Patients negative for PHA with basal CAP ARR > 50 or low renin levels were diagnosed with AAH. MRB (50–100 mg spironolactone or 200–300 mg eplerenone) as sole BP medication. BP (mmHg), Mann-Whitney U; Student’s t, and Wilcoxon, χ2 tests 15.

Results
Baseline characteristics HAP vs AAH: 28/60 vs 32/60 patients, 67.9% vs 75% women, mean age 55.4 (S.D.: 7.2) vs 53.9 (S.D.: 9.3). Number BP-lowering drugs: 2 (IQR: 1–2) vs 1 (IQR: 1–2). Resistant hypertension (RH): 6/21 (24.4%) vs 2/32 (6.3%). Major CV events and/or renal failure: 8/28 (28.6%) vs 5/32 (15.6%), P = 0.06. Hypokalemia: 5/28 (17.8%) vs 3/32 (9%), P = 0.003. Serum potassium (mmol/l) (SK): 4.0 (S.D.: 0.6) vs 4.2 (S.D.: 0.5) (t: 3.5–5.5), serum creatinine (mg/dl) (SC): 1.0 (S.D.: 0.5) vs 0.89 (S.D.: 0.3), systolic BP (SBP): 154 (S.D.: 22.6) vs 151 (S.D.: 16.6), diastolic BP (DBP): 90 (S.D.: 14.4) vs 90 (S.D.: 12.1). Response to 2 weeks of MRB: SBP 128 (S.D.: 15.7) vs 123 (S.D.: 11.8), DBP: 77 (S.D.: 10.7) vs 75 (S.D.: 9.1); SK: 4.6 (S.D.: 0.5) vs 4.7 (S.D.: 0.5); SC: 1.14 (S.D.: 0.7) vs 1.00 (S.D.: 0.4). The descent in both SBP and DBP was significant in PHA (both P < 0.001) as in AAH (both P < 0.001). No significant differences were found in SBP (P = 0.569) or DBP (P = 0.389) reductions following MRB in PHA vs AAH.

Conclusion
The CAP can identify both patients with PHA and AAH. Both groups present a similar, dramatic and rapid BP response to high-dose MRB, suggesting that AAH patients should be identified, and the same protocol for medical therapy used in PHA and AAH. Furthermore, our results support the hypothesis that aldosterone-induced hypertension is a continuum.

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GP03.06
Applying a new decision threshold to an old test: does the measurement of plasma metanephrines in patients fasting and supine improve diagnostic sensitivity?
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The recently published Endocrine Society Clinical Practice guideline on pheochromocytoma and paraganglioma (PPGL) recommends measuring plasma metanephrines (PMEts) with patients in the supine position after an overnight fast and using appropriately defined reference intervals. Studies have shown higher diagnostic sensitivities using the latter pretesting criteria. However, this testing protocol is resource intensive and arguably impractical in routine clinical practice. In our institution blood samples for PMets are collected with patients non-fasting and seated using reference intervals established accordingly. The aim of the present study was to assess the effects on diagnostic test performance retrospectively in patients who underwent PMets screening in our institution between 2009 and 2014 using reference intervals derived in subjects fasting and supine. A total of 150 patients were included in this study. There were 79 males (53%) and 71 females (47%). The mean age was 54.3 years (s.d.: 6 years). A total of 45 (30%) patients would have had a positive test result based on the supine reference interval being applied vs a total of 8 (5.3%) patients who screened positive using the decision thresholds derived in seated subjects. There were 6 (4%) patients with histologically confirmed PPGL in this cohort and no case would have been missed using the non-fasting and seated reference intervals for PMets. The most common alternative diagnosis for the 39 patients who screened positive for PMets using the new supine reference interval but who did not have a diagnosis of PPGL was essential hypertension (n=19, 48.7%). This study demonstrates that the existing, more pragmatic pretesting protocol for PMets collection resulted in no false-negative biochemical screening for PMets over a 5-year period and that application of a supine reference interval would have resulted in 39 false-positive results in this same time period.

References

DOI: 10.1530/endoabs.37.GP.03.06

GP03.07
Comparison of urinary metanephrine concentrations after unilateral adrenalectomy for pheochromocytoma to healthy subjects
Yoon Young Cho, Dong Ik Cha, Jae Hoon Chung, Sun Wook Kim & Jae Hyeon Kim
Samsung Medical Center, Seoul, Republic of Korea.

Background
Urinary metanephrine (MN) and normetanephrine (NMN) are used to detect recurrence of pheochromocytoma during post-operative period. Currently, reference ranges of urinary MN and NMN obtained from healthy individuals are applied to subjects with adrenaleucotomy. However, studies regarding the use of reference ranges from healthy subjects in pheochromocytoma patients with adrenaleucotomy are limited.

Aim
To compare urinary MN and NMN concentrations in patients after unilateral adrenalectomy to concentrations in healthy subjects.

Methods
A single-center retrospective study was conducted in pheochromocytoma patients confirmed with pathology. Eighty-two patients underwent unilateral adrenalectomy between February 2004 and June 2014 and had no evidence of recurrence during follow-up period. Urinary MN and NMN were checked before and after surgery with 3- or 6-month-intervals.

Results
Urinary MN concentration after unilateral adrenalectomy was lower than control group (70.0 μg/day vs 92.0 μg/day, P < 0.001), whereas urinary NMN was not

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different (220.9 μg/day vs 232.0 μg/day). According to post-operative period, urinary NMN determined in immediate post-operative period (within 1 month after surgery) was higher than the concentration in the period between 12 and 36 months (287.3 μg/day vs 204.0 μg/day, P < 0.01). Urinary MN in male subjects was higher compared to the concentration in female subjects (81.0 μg/day vs 64.8 μg/day, P < 0.01).

Conclusions
Urinary MN concentration in phaeochromocytoma patients after unilateral adrenalectomy was lower than the concentration in control group. Different reference ranges of urinary MN are needed for post-operative phaeochromocytoma patients. Urinary NMN was not different in both groups, however tendency that the concentration was higher in immediate post-operative period was observed.

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GP.03.08
Obstructive sleep apnea presenting as pseudopheochromocytoma
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Introduction
The obstructive sleep syndrome (OSAS) has a well-documented association with increase cardiovascular morbidity and mortality. The patients with OSAS have a high prevalence of hypertension (HTA).

Case report
A 52-year-old female with a history of poorly controlled resistant HTA was admitted to our hospital with severe HTA. She had a history of fatigue and intermittent episodes of palpitations. Laboratory evaluation was significant for elevated 24-h urinary catecholamine levels (CU = 3.5 μg/24 h). This case was presenting with a clinical and biochemical picture indistinguishable from that of phaeochromocytoma. However, neither computed tomography nor MIBG scintigraphy detected any catecholamine-producing tumor in or outside the adrenal glands. Our patient was screened with full polysomnography because of heavy snoring, daytime somnolence, and obesity. It revealed severe (OSAS).

After three months of continuous positive airway pressure therapy, the patient improved with a significant reduction in heart rate variability and less frequent palpitations. The use of continuous positive airway pressure therapy stopped most of the symptoms. No further investigations were repeated.

In this observation, we report a case of pseudo phaeochromocytoma; a potentially reversible cause of pseudo phaeochromocytoma.

GP.04.02
The modulation of corticosteroid metabolism by hydrocortisone exposure in patients with hypopituitarism increases tissue glucocorticoid exposure
Mark Sherlock1,2,3, Lucy Ann Behan4, Mark Hannon5, Aurora Aragon Alonso4, Christopher Thompson6, Robert Murray7, Nicola Crabtree8, Beverly Hughes9, Wiebke Arli10, Amaa Agha11, Andrew Toogood12 & Paul M Stewart13
1Centre for Endocrinology, Diabetes and Metabolism, University of Birmingham, Birmingham, UK; 2Department of Endocrinology and Diabetes, Adelaide and Meath Hospitals, Incorporating the National Children’s Hospital, Dublin, Ireland; 3School of Sport and Exercise Science, University of Birmingham, Birmingham, UK; 4Department of Nuclear Medicine, Queen Elizabeth Hospital, Birmingham, UK.

Context
Patients with hypopituitarism have increased morbidity and mortality. There is ongoing debate around the optimum glucocorticoid replacement therapy.

Objective
To assess the effect of glucocorticoid replacement in hypopituitarism on corticosteroid metabolism and its impact on body composition.

Design and patients
To assess the urinary corticosteroid metabolite profile (using gas chromatography/mass spectrometry) and body composition (clinical parameters and full body DXA) of 53 patients (19 females, median age 46 years) with hypopituitarism (33 ACTH deficient/20 ACTH replete) (study A). The corticosteroid metabolite profile of ten patients with ACTH deficiency was then assessed prospectively in a cross over study using three hydrocortisone dosing regimens (20/10, 10/10, and 10/5 mg) (study B) each for 6 weeks. 11β-HSD1 activity was assessed by urinary THF+5α-THF/THE.

Setting
Endocrine Centres within University Teaching Hospitals in UK and Ireland.

Main outcome measures
Urinary corticosteroid metabolite profile and body composition assessment.

Results
In study A, when patients were divided into three groups: patients not receiving HC, patients receiving HC < 20 or ≥ 20 mg/day, patients in the group receiving the highest daily dose of HC had significantly higher WHR than the ACTH replete group. They also had significantly elevated THF+5α-THF/THE (p = 0.0002) and total cortisol metabolites (P = 0.015). In study B, patients on the highest hydrocortisone dose had significantly elevated total cortisol metabolites and all patients on hydrocortisone had elevated THF+5α-THF/THE ratios when compared to controls.

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Conclusions
In ACTH deficient patients daily HC doses of >20 mg/day have increased WHR. THF + 5α-THF/THE ratios and total cortisol metabolites. Glucocorticoid metabolism and induction of 11β-HSD1 may play a pivotal role in the development of the metabolically adverse hypopituitary phenotype.

DOI: 10.1530/endoabs.37.GP.04.02

GP.04.03
Using a morning cortisol to predict adrenal reserve and guide management
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Background
The short Synacthen test (SST) is the most widely used dynamic assessment of adrenal reserve. In some situations, the SST may be difficult to perform. Random basal cortisol levels could provide an alternative screening assessment to rationalize which patients need dynamic testing. This is highly clinically relevant, given the large numbers of patients taking prescribed glucocorticoids who are at risk of iatrogenic adrenal suppression.

Methods
3603 SST results (all performed in the morning) were analysed from electronic records in a large secondary/tertiary centre across all specialities. A 30 min cortisol value >549 nmol/l was defined as a pass. Results were divided into subgroups including age, sex, pituitary, and adrenal pathology and patients taking inhaled corticosteroids (ICS). Receiver operator characteristic curves were used to generate area under the curve (AUC), best-fit cortisol values and to predict cut-off values for specificities and sensitivities.

Results
Baseline and 30 min cortisol levels correlate positively (r = 0.74, P < 0.0001). Basal cortisol levels >440 and ≥506 nmol/l gave 99 and 100% specificity respectively for passing the SST. Baseline cortisol <107 nmol/l gave a 99% sensitivity for failing. Cut-off values and AUCs were similar between groups divided by sex, age, and menopausal status. In patients currently taking ICS, 31% failed an SST (71/226). Patients taking ICS with a basal cortisol ≥359 nmol/l (36%, n=81) passed, and those with a cortisol <354 nmol/l (4%, n=9) failed an SST. In post-pituitary surgery patients (n = 329), those with basal cortisol above 350 nmol/l (23%) passed, and those below 46 nmol/l (11%) failed the SST.

Conclusion
Baseline cortisol levels can be informative in predicting the SST response. A high clinical index of suspicion of adrenal insufficiency mandates dynamic assessment of adrenal reserve by SST. However, a basal cortisol may have a clinical utility in discrete patient cohorts, such as those on ICS, in whom, within our cohort, 40% (n=90) of SSTs could have been avoided.

Disclosure
This work has been supported by the Medical Research Council (Senior Clinical Fellowship ref. G08002765, J Tomlinson).

DOI: 10.1530/endoabs.37.GP.04.03

GP.04.04
Regulation of lipogenesis in human hepatocytes by androgens, glucocorticoids, and 5α-reductase
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12nd Department of Internal Medicine, Semmelweis University, Budapest, Hungary; 2Lendület Hereditary Endocrine Tumours Research Group, Budapest, Hungary; 3Molecular Medicine Research Group, Hungarian Academy of Sciences, Semmelweis University, Budapest, Hungary; 4Department of Laboratory Medicine, Semmelweis University, Budapest, Hungary.

Objective
Glucocorticoids exert their effects through the glucocorticoid receptor (GR). The local, cell-type specific glucocorticoid effect is modulated by the 11β-hydroxysteroid dehydrogenase enzymes (HSD11B1) responsible for the interconversion of cortisone and cortisol. Individual sensitivity against glucocorticoids and activity of the HSD1B1 enzymes are at least partly determined by genetic factors.

Aim
To test whether SNPs of GR and HSD11B1 genes (N363S-r6195, Bcll-rs41423247, A3669G-r6198 of GR; and rs2086634, rs4484880 of HSD11B1) influence the glucocorticoid replacement dosage, and clinical/laboratory parameters in patients with Addison’s disease.

Patients and methods
67 patients with primary adrenal insufficiency diagnosed and treated at the 2nd Department of Medicine, Semmelweis University were studied. Clinical, laboratory data, and the dosage of the hormone replacement therapy were collected. Peripheral blood DNA was isolated, and the GR gene SNPs were examined using allele-specific PCR (for Bcll and N363S) or TaqMan assay on real-time PCR (for A3669G, rs2086634, and rs4484880). Genotype distribution was compared to those observed in the general Hungarian population using χ² or Fischer exact t-test. ANOVA followed by power analysis was used for association studies.

Results
The allele frequency of N363S polymorphism was higher in patients compared to the control group. Among GR gene SNPs only the Rs11 polymorphism associated with BMI; the number of homozygous carriers was significantly higher than that of heterozygous carriers or non-carriers (P = 0.007, power: 100%). The disease appeared significantly earlier in patients harboring A3669G SNP. The rs4484880 SNP associated with higher BMI and with higher bodyweight-adjusted glucocorticoid substitution dose, the disease developed in significantly later age in these patients. Annual decrease of bone mineral density, t-score and z-score at lumbar spine was significantly lower in carriers compared to non-carriers.

Conclusion
SNPs of GR and HSD11B1 genes may be important genetic factors in the pathogenesis and therapy-related morbidities in patients with primary adrenal insufficiency.
In recent years measurement of steroid hormones like testosterone, androstenedione, cortisol, and cortisone has become increasingly important in both patient care and research. This is mainly due to the simple and non-invasive sample collection. We investigated in twenty healthy volunteers whether there is a difference between steroid hormone concentrations in unstimulated and parotid gland saliva as well as stimulated saliva collected while chewing without aid, using cotton and synthetic Salivettes, citric acid, or chewing gum. Testosterone, androstenedione, cortisol, and cortisone were measured in all saliva samples using ion-pair dilution liquid chromatography–tandem mass spectrometry (ID- LC-MS/MS). Testosterone, androstenedione, and cortisol concentrations were not affected by stimulation by chewing itself, whereas cortisol levels decreased (mean decrease was 11%). Levels of all four hormones were lower in parotid gland saliva compared to unstimulated saliva (mean decrease was 27, 14, 24, and 27% respectively). Salivary levels of testosterone, androstenedione, and cortisol decreased when using synthetic Salivettes (mean decrease was 56, 38, and 25% respectively) and increased when using cotton Salivettes (mean increase was 238, 50, and 34% respectively) compared to chewing without aid, whereas cortisol levels in saliva were unaffected by both types of Salivettes. Citric acid stimulation decreased salivary cortisol levels (mean decrease was 35%). Chewing gum decreased cortisol levels (mean decrease was 25%). In conclusion, the way saliva is collected should be taken into account when analysing and interpreting salivary hormone concentrations. Parotid gland saliva has lower steroid hormone levels than total saliva. Stimulation on its own does not change the concentrations of testosterone, androstenedione, and cortisol, but decreased the levels of cortisone. This is probably due to the rate-limited conversion of cortisol to cortisone in salivary glands. Stimulation with Salivettes, should be avoided for analysis of testosterone, androstenedione, and cortisone. Stimulation with citric acid and chewing gum are not suitable for analysis of cortisone.

**Table 1**

<table>
<thead>
<tr>
<th>Testosterone, androstenedione, cortisol, and cortisone levels in unstimulated, stimulated, and parotid saliva</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rahel M Büttler1, Esra Bagci1, Henk Brand1, Marinus A Blankenstein1 &amp; Annemieke C Heijboer1</td>
</tr>
<tr>
<td>1Endocrine Laboratory, Department of Clinical Chemistry, VU University Medical Center, Amsterdam, The Netherlands; 2Departments of Periodontology and Oral Biochemistry, Academic Centre for Dentistry Amsterdam (ACTA), Amsterdam, The Netherlands.</td>
</tr>
</tbody>
</table>

**GP.04.06**

Testosterone, androstenedione, cortisol, and cortisone levels in unstimulated, stimulated, and parotid saliva

<table>
<thead>
<tr>
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In recent years measurement of steroid hormones like testosterone, androstenedione, cortisol, and cortisone has become increasingly important in both patient care and research. This is mainly due to the simple and non-invasive sample collection. We investigated in twenty healthy volunteers whether there is a difference between steroid hormone concentrations in unstimulated and parotid gland saliva as well as stimulated saliva collected while chewing without aid, using cotton and synthetic Salivettes, citric acid, or chewing gum. Testosterone, androstenedione, cortisol, and cortisone were measured in all saliva samples using ion-pair dilution liquid chromatography–tandem mass spectrometry (ID- LC-MS/MS). Testosterone, androstenedione, and cortisol concentrations were not affected by stimulation by chewing itself, whereas cortisol levels decreased (mean decrease was 11%). Levels of all four hormones were lower in parotid gland saliva compared to unstimulated saliva (mean decrease was 27, 14, 24, and 27% respectively). Salivary levels of testosterone, androstenedione, and cortisol decreased when using synthetic Salivettes (mean decrease was 56, 38, and 25% respectively) and increased when using cotton Salivettes (mean increase was 238, 50, and 34% respectively) compared to chewing without aid, whereas cortisol levels in saliva were unaffected by both types of Salivettes. Citric acid stimulation decreased salivary cortisol levels (mean decrease was 35%). Chewing gum decreased cortisol levels (mean decrease was 25%). In conclusion, the way saliva is collected should be taken into account when analysing and interpreting salivary hormone concentrations. Parotid gland saliva has lower steroid hormone levels than total saliva. Stimulation on its own does not change the concentrations of testosterone, androstenedione, and cortisol, but decreased the levels of cortisone. This is probably due to the rate-limited conversion of cortisol to cortisone in salivary glands. Stimulation with Salivettes, should be avoided for analysis of testosterone, androstenedione, and cortisone. Stimulation with citric acid and chewing gum are not suitable for analysis of cortisone.

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**Description of methods**

165 patients with systemic lupus erythematosus (32.1% patients), systemic vasculitis (27.3% patients), and chronic glomerulonephritis (40.6% patients) were included. 98 patients received GC pulse-therapy (GCPT) (first group), which included i.v. infusion of prednisolone 10–15 mg/kg per day with 250 ml of 0.9% NaCl solution, on 3 consecutive days; course dose was 1800–3000 mg; 67 patients (second group) received oral GC therapy 15–30 mg/day. All patients passed an oral glucose tolerance test (OGTT) after the course of GCPT in the first group and after 5 days of hospital stay in the second group. An evaluation of CMD was performed.

**Results**

The study revealed that the incidence of CMD depends on the mode of GC therapy and does not depend on the type of immunoinflammatory disease. CMD was more prevalent in patients receiving oral GC therapy. CMD was observed in 33 (33.7%) patients, receiving GCPT and in 54 (80.6%) patients, receiving oral GC (P = 0.035). Impaired fasting glucose (IFG) (> 7.8 mmol/l 2 h after OGTT, high fasting glucose at baseline 5.5–6.1 mmol/l) was found with similar incidence in first and second groups (8 (8.2%) and 14 (20.9%), respectively, P = 0.069). Impaired glucose tolerance (7.8–11.1 mmol/l 2 h after OGTT) and diabetes mellitus (≥ 11.1 mmol/l 2 h after OGTT) were more prevalent in the second group – in 21 (31.3%) and 19 (28.4%) patients, compared to 13 (13.3%) and 12 (12.2%) patients in the first group respectively (P = 0.038 and P = 0.049).

**Conclusions**

CMD develop more often in patients with immunoinflammatory diseases receiving long-term oral GC therapy, compared to patients on GCPT. All patients should be regularly screened for CMD and receive necessary correction.

**DO**: 10.1530/endoabs.37.GP.05.04

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**Developmental and paediatric endocrinology**

**GP.05.01**

**Regulation of murine skeletal muscle mass by testosteron and 17β-oestradiol**

Ryan Paul1,2, Chris McMillon, Marianne Elston1 & John Conaglen1

1Department of Medicine, Waikato Clinical School, University of Auckland, Hamilton, New Zealand; 2Agriculture, Ruakura, New Zealand.

The predominant positive and negative regulators of skeletal muscle mass are IGF1 and myostatin respectively. The regulation of skeletal muscle mass, IGF1 and myostatin by the gonadal steroids testosteron and 17β-oestradiol (E2) remains controversial. Male and female C57BL/6 mice underwent bilateral gonadectomy or sham surgery at 4 weeks of age, with insertion of s.c. silastic implants containing testosteron, E2, or cholesterol (placebo) (n = 8/treatment and sex). Blood and hindlimb muscles were collected at 13 weeks of age and muscle mass was normalised to bone length. Concentrations of IGF1 in plasma were determined by ELISA. C2C12 myoblasts were treated under differentiating conditions with testosteron (30 nM) or E2 (10 nM) for 24 h and RNA was harvested for quantitative PCR. Myoblasts were also treated for 96 h and differentiation was assessed by immunocytochemistry. Sexual dimorphism of normalised hindlimb muscle mass was lost post-gonadectomy. In male mice, gonadectomy reduced normalised hindlimb muscle mass, reduced IGF1 mRNA expression and increased mature myostatin protein abundance (P < 0.001). Replacement of testosteron normalised these parameters, while replacement of E2 only normalised hindlimb muscle mass. Concentrations of IGF1 in plasma were not altered by any treatment in males. In female mice, gonadectomy + E2 replacement did not alter normalised hindlimb muscle mass or mature myostatin protein abundance, despite reducing concentrations of IGF1 in plasma and skeletal muscle (P < 0.05). Testosteron significantly increased normalised hindlimb muscle mass, increased concentrations of IGF1 in plasma and skeletal muscle, while reducing the abundance of mature myostatin. Testosteron significantly increased myotube hypertrophy (151%) to a greater extent than E2 (61%); although, neither altered IGF1 mRNA expression. We conclude that the anabolic action of testosteron on skeletal muscle is partially through modulation of IGF1 and myostatin activity. However, E2 appears to increase skeletal muscle mass independently of IGF1 or myostatin.

**Disclosure**

Waikato Medical Research Foundation (grant number 223).

**DO**: 10.1530/endoabs.37.GP.05.01

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**GP.05.02**

The differential impact of PAPS synthease isoforms on DHEAS may be explained by an isoform-specific interaction of SULT2A1 with PAPS2, but not PAPS1

Jon W Mueller1, Jan Ikdowiak1, Rebecca E Hardman1, Philip J House1, Joanne C McNelis1, Ian T Rose1, Vivek Dhir1, Edina Ronin2 & Wibeke Arlt1

1CEDAM, University of Birmingham, Birmingham, UK; 2Department of Chemistry, King’s College London, London, UK.

Human sulfation depends on provision of the universal sulfate donor PAPS by the two PAPS synthease isoforms PAPS1 and PAPS2. Mutations in PAPS2 have been identified as a monogenic cause of androgen excess presenting with premature adrenarche and polycystic ovary syndrome, due to decreased sulfation of the androgen precursor DHEA by DHEA sulfotransferase (SULT2A1) and hence increased conversion of DHEA to active androgens (New Eng J Med 2006 340 (22) 2210–2318 and J Clin Endocrinol Metab 2015 jc12014556). Here, we examined why ubiquitously expressed PAPS1 cannot compensate for the impact of PAPS2 deficiency on DHEAS. First, we carried out siRNA-mediated knockdown of PAPS1/2 in the adrenal cell line NCI-H295R. Real-time PCR confirmed >90% knockdown and the impact at protein level was assessed by western blot and SULT2A1 activity assays. Efficient knockdown of PAPS2 reduced DHEAS to 30 ± 5%. Strikingly, PAPS1 knockdown did not impact on DHEAS, providing in vitro evidence for non-overlapping functionality of the two PAPS isoforms. To test whether subcellular localisation impacts on isoform-specific capacity to support DHEAS, we used HEK293 cells to co-express SULT2A1 with either WT PAPS1/2 or exclusively nuclear or cytoplasmatic PAPS1/2 variants. WT and nuclear PAPS1/2 equally supported DHEAS; however, SULT2A1 activity with exclusively cytoplasmic expression of PAPS2 was 1.6-fold higher than with cytoplasmic PAPS1; suggesting an isoform-specific protein-protein interaction of SULT2A1 with PAPS2, but not PAPS1. To examine this further, we carried out docking studies using ClusPro. Z-dock and gromm-X servers employing the Akin kinase protein structures 2ofx and 2ax4 for PAPS1/2 and three different structures for human SULT2A1 (1efh, 3f3y, and 4ifb). Docking of SULT2A1 to PAPS2 uniformly resulted in more homogeneous complexes than for SULT2A1– PAPS1, yielding significantly higher scores by the associated docking algorithms. Such an isoform-specific interaction with SULT2A1 may be the underlying mechanism explaining why PAPS2 deficiency results in disruption of DHEAS despite ubiquitous expression of PAPS1. Follow-up studies to prove direct interaction of PAPS2 and SULT2A1, employing pulldown assays and FRET analyses, are currently underway.

**Disclosure**

Marie Curie IEF award 625431 SUPA-HD (to J W Mueller) and Wellcome Trust project grant 092283 (to W Arlt).

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**GP.05.03**

Determination of the topology of microsomal 17β-hydroxysteroid dehydrogenase enzymes using redox-sensitive green fluorescence protein fusions

Maria Tsachaki, Julia Birk & Alex Odermatt

University of Basel, Basel, Switzerland.

Membrane proteins of the endoplasmic reticulum (ER) are involved in a wide array of essential cellular functions. Identification of the topology of membrane proteins can provide important insight into their mechanisms of action and biological roles. This is particularly important for membrane enzymes, since their topology determines the subcellular site where a biochemical reaction takes place and the dependence on luminal or cytosolic substrates and co-factor pools. The methods currently available for the determination of topology of proteins are rather laborious and require post-lysis or post-fixation manipulation of cells. In this work, we have developed a novel and simple method for defining intracellular localisation and topology of ER membrane proteins in living cells, based on the fusion of the respective protein with redox-sensitive green fluorescent protein (roGFP). We validated the method and demonstrated that roGFP fusion proteins constitute a reliable tool for the study of ER membrane protein topology, using as control microsomal 11β-hydroxysteroid dehydrogenase (11β-HSD) proteins whose topology has been resolved, and comparing with an independent approach. We then implemented this method to determine the membrane topology of six microsomal members of the 17β-HSD family. 17β-HSD enzymes catalyse the reduction/oxidation at the position 17 of the steroid backbone of androgens and oestrogens, thus playing a key role in the control of the balance of active and inactive sex steroids. Many 17β-HSDs have been implicated in different forms of sex-specific cancer and 17β-HSD inhibitors have attracted considerable interest as therapeutic targets. Appropriate access of such inhibitors to the respective intracellular compartment needs to be considered in drug development. Our

**Disclosure**

The authors have no conflicts of interest to declare.

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results revealed a luminal orientation of the catalytic site for three 17β-HSD enzymes. Knowledge of the intracellular location of the catalytic site of these enzymes will enable future studies on their biological functions and roles in human diseases.

Disclosure

Swiss National Foundation.

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GP.05.04

Pilot study on the effects of cross-sex hormone treatment in transsexual persons on metabolism by means of metabolomics profiling

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1Endocrinology, Diabetology and Internal Medicine, Max Planck Institute of Psychiatry, Munich, Germany; 2Research Unit of Molecular Epidemiology, Helmholtz Zentrum München, Neuhberg, Germany; 3Institute of Experimental Genetics, Genome Analysis Center, German Center for Diabetes Research, Neuherberg, Germany; 4Department of Endocrinology, Ghent University Hospital, Ghent, Belgium.

Introduction

Sex steroid hormones exert a wide range of effects on metabolism. New techniques such as metabolomic profiling allow for a deeper insight into metabolic regulation. In some endocrinological samples it has been demonstrated that most of these metabolites show sex-specific differences. However, if these differences are attributable to the effects of sex hormones or genetics is little understood so far.

Methods

We performed targeted metabolomics profiling in serum of fasting transmen (F2M) and transwomen (M2F) at baseline and following 12 months of cross-sex hormone treatment (n = 20/group). Subjects investigated in this study were part of the European Network for the Investigation of Gender Incongruence (ENIGI). The targeted metabolomics approach was based on ESI–LC–MS/MS measurements by AbsoluteIDQTM p180 Kit (Biocrates Life Sciences AG).

Results

Several metabolites concentrations changed significantly between the two visits in the M2F group including l-carnitine, octadecan-1-l-carnitine, threonine, alpha-amino adipic acid, hydroxyproline, phosphatidylcholine diaeryl C34:3, ornithine, citrulline, and ornithine/arginine ratio (FDR <0.05, P <0.05). In the F2M group there was only a significant change in ornithine. After adjustment for age, lifestyle factors and body composition in a linear mixed effects model, these results remained significant but vanished after adjusting for sex hormone levels. This indicates a direct effect of sex hormones on metabolite levels. Opposite effects were seen, i.e. for changes in ornithine levels between the two groups. Ornithine was further strongly positively related to testosterone levels in both groups. These findings are also in line with the sex-specific dimorphism for metabolites observed in epidemiological studies.

Conclusion

In this first pilot study we could show that cross-sex hormone treatment induces several changes in serum metabolites. Our findings indicate a direct effect of sex hormones on different metabolic cycles including lipid metabolism, nitric oxide formation, and amino acid regulation.

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GP.05.05

Does the initiation of oestrogen therapy time affect final height and late metabolic outcomes in Turner syndrome?

Ruta Kriskiuciene1,2, Birute Zilaitiene1,2, Rima Berontiene1,2, Ruta Nakaite2, Jurate Drazdauskaite2 & Rasa Verkauskiene1
1Hospital of Lithuanian University of Health Sciences Kauno Klinikos, Kaunas, Lithuania; 2Lithuanian University of Health Sciences, Kaunas, Lithuania.

Aim

To compare final height and late metabolic outcomes depending on oestrogen replacement initiation in Turner syndrome (TS).

Subjects

Women with TS ≥18 years retrospectively treated with GH and oestrogen.

Methods

Records of 117 women with TS from database of Hospital of Lithuanian University of Health Sciences were analysed. 71 did not matched the inclusion criteria; 46 patients were enrolled and divided into two groups: early oestrogen group (E1) – E1 before 15 years (n = 27, E1 at a median of 13 years, range from 13 to 14 years) and delayed oestrogen group (E2) – E2 ≥15 years (n = 19, E2 at a median of 16 years, range 16–18 years). Final height, height gain, BMI, fasting glucose, blood pressure, and bone density was compared between the groups.

Results

GH treatment was started at a median age of 11 years (range 9–12 years) in the E1 and of 15 years (range 9.25–16.75 years) in the E2 group (P <0.005). The final height was similar in both groups: median of 153 cm (range 148–156 cm) in the E1 and 152 cm (range 147–155 cm) in the E2 (P <0.055). The height before E1 in the E1 group was −2.26 and −2.90 SDS in E2 group (P <0.055). Height gain was greater (P <0.05) in E1 (median 11.7 cm, range 7.1–15 cm) than in E2 (median 5.23 cm, range 2.5–8.1 cm) group. No significant differences in metabolic parameters have been identified between the groups (mean age 27 ± 5.6 years).

Conclusion

Puberty induction at a physiological age does not have negative effect on final height in TS patients, providing earlier start of oestrogen treatment. No relation between oestrogen initiation time and metabolic parameters during later life span had been found.

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GP.05.06

Comparison of seven LC–MS/MS methods for the simultaneous measurement of testosterone, androstenedione, and DHEA in serum

Rahel M Büttler1, Frans Martens1, Flaminia Fanelli2, Brian G Keevil3, Hai T Pham4, Mark M Kushnir5, Angela E Taylor6, Tue Soeborg7, Marinus A Blankenstein1 & Annemieke C Heijboer1
1Endocrine Laboratory, Department of Clinical Chemistry, VU University Medical Center, Amsterdam, The Netherlands; 2Endocrinology Unit, Department of Medical and Surgical Sciences, Center for Applied Biomedical Research, S. Orsola Malpighi Hospital, University of Bologna, Bologna, Italy; 3Department of Clinical Biochemistry, University Hospital of South Manchester, Manchester, UK; 4Biocrates Life Sciences AG, Innsbruck, Austria; 5Department of Pathology, ARUP Institute for Clinical and Experimental Pathology, University of Utah, Salt Lake City, Utah, USA; 6School of Clinical and Experimental Medicine, Centre for Endocrinology, Diabetes and Metabolism, University of Birmingham, Birmingham, UK; 7Department of Growth and Reproduction, Faculty of Health and Medical Sciences, Rigshospitalet, Copenhagen University Hospital, University of Copenhagen, Copenhagen, Denmark.

Recently, liquid chromatography–tandem mass spectrometry (LC–MS/MS) was stated to be the method of choice to measure sex steroids. Information on the mutual agreement of LC–MS/MS methods, however, is scarce. Therefore, we compared seven published LC–MS/MS methods for the simultaneous measurement of testosterone, androstenedione, and DHEA in serum by AbsoluteIDQ™ p180 Kit (Biocrates Life Sciences AG).

Introduction

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DOI: 10.1530/endoabs.37.GP.05.04

Comparison of seven LC–MS/MS methods for the simultaneous measurement of testosterone, androstenedione, and DHEA in serum

GP.05.07
Prediction of affective disorders in adult men on the basis of steroid profiling
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1Institute of Endocrinology, Prague, Czech Republic; 2National Institute of Mental Health, Kleeany, Czech Republic.

A number of evidence indicate that mood (affective) disorders are influenced by various bioactive steroids such as corticoids, sex hormones and neuroactive steroids. However, to date, there are limited data concerning the discrimination between patients suffering from the disorders and controls, or regarding the classification of individual subtypes of mood disorders on the basis of steroid profiling. Therefore 47 steroids including their conjugates and further related substances were measured in sera from male volunteers suffering from depressive disorders (D, n = 20), anxiety disorders (AN, n = 20), and in the group of age-comparable controls (C, n = 30) using GC–MS and immunnoassays. Based on this data, multivariate models for discrimination of D and C (sensitivity = 100% and specificity = 100%), AN and C (sensitivity = 100% and specificity = 100%), and D and AN (sensitivity = 85% and specificity = 90%) were built. When discriminating pathologies D and AN from C, the relevant predictors progesterone, allopregnanolone, and conjugated steroids negatively correlated with both AN and D groups, while LH showed the positive correlations. In addition, 5α-dihydrotestosterone and pregnenolone negatively correlated with D, while androstenedione, cortisol, 16α-hydroxy-steroids, and SHBG showed the positive correlations. Finally, pregnenolone, 20α-dihydroprogrenolone, 7β-hydroxy-DHEA, and 5-androstene-3β,7α,17β-triols positively correlated with AN. In model discriminating D and AN, the relevant predictors progesterone and cortisol positively correlated with AF, while LH, SHBG, sulphated Δ4 steroids, and 16α-hydroxy-DHEA showed the negative correlations. In conclusion, various circulating steroids including the neuroactive and neuroproactive ones efficiently predicted two groups of affective disorders in adult men. The data indicated suppressed activities of CYP17A1 and SULT2A1 enzymes in adrenal zona reticularis in affective patients and even more in depressive men. In addition, the results pointed to stimulated activities of immunomodulatory 16α-hydroxylating (CYP17A) and 7β-hydroxylating enzymes (CYP3A4) in D and AN patients respectively.

Disclosure
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GP.05.08
A simple and rapid method for steroid profiling by two dimensional liquid chromatography–tandem mass spectrometry: toward routine application
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Steroid testing has a central role in clinical decision-making and in research studies on diseases such as hypercortisolism, female hyperandrogenism, male hypogonadism or inborn disorders of steroid synthesis. Recently, liquid chromatography–tandem mass spectrometry (LC–MS/MS) proved its superiority to routine immunoassays (IA) in accurately and sensitively measuring low level steroids. However, the replacement of automated IA with LC–MS/MS platforms is limited by the need for extraction procedures requiring operator handwork, large sample volume and long runtime. Aiming at improving LC–MS/MS practicability, we developed a 2D-LC–MS/MS method for simultaneously determining serum cortisol, testosterone, androstenedione, 17OHPregesterone (OHP), and 17OHpregnenolone (OHP) based on minimal sample preparation. One hundred μl of serum were treated by protein precipitation, diluted with H2O and injected into the Prominence-LCMS-8050-electrospray ionisation platform (Shimazu). Sample pretreatment on-line purification on partition column (6 ml/min, 3 min) and separation on Shim-pack XR-ODS-53 × 3 mm, 2 μm column (Shimadzu) in 5 min H2O/Octamethyltril (gradient, before 7 min clean-up and reconditioning process. Total runtime was 15 min. Quantitative and qualitative transitions were monitored for each analyte. Isotopic dilution quantitation was performed by using d4-cortisol, d5-testosterone, d5-androstenedione, d8-OHP, and 13C3-estrone as internal standard for cortisol, testosterone, androstenedione, OHP, and OHP respectively. Lower limits of quantitation (pg on column) assessed in calibrators diluted in BSA (%v/v) were 122.1 pg/ml (1.5 pg), 9.77 pg/ml (0.12 pg), 19.5 pg/ml (0.24 pg), 39.1 pg/ml (0.49 pg), and 312.5 pg/ml (3.5 pg), and functional sensitivity assessed in charcoal-stripped serum was 122.1, 19.5, 19.5, 39.1, and 312.5 pg/ml for cortisol, testosterone, androstenedione, OHP, and OHP respectively, and was stable along 150 samples batch. Intra- and inter-assay CV ranged between 3.4–7.2% and 5.8–16.7% respectively. Analyte-internal standard comparison with an established extractive LC–MS/MS assay revealed optimal correlation (r: 0.9933–0.9996) and slope coefficients (0.810–1.060). These preliminary data showed that our 2D-LC–MS/MS method for five steroids based on minimal sample preparation achieves performance and robustness levels that can definitively reconcile routine need for reliability and practicability.

Disclosure
This work was supported by the Emilia Romagna Region-University Program for Young Investigators ‘Alessandro Libertini’ 2010–2012 PRUA 1–2012-004. DOI: 10.1530/endoabs.37.GP.05.08

GP.05.09
Investigation of the effects of aldosterone on the cardiac cycle in the HL-1 mouse atrial cardiomyocyte cell line
Kostantinos Tsirlis1, Anastasios Tsarouhas1, Eleni Aggelidou1, Efstratios Kosmidis2, Aristides Kritis1, Maria Alban1 & Konstantinos Kalantaras1
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Introduction
Aldosterone (Aldo) decreases the rate of repolarization in rabbit cardiomyocytes and significantly increases the duration of the monophasic action potential in patients with supraventricular arrhythmias, few minutes after its intravenous administration, implying for a non-genomic action. We have previously found a positive linear regression between left ventricular systole duration and plasma Aldo levels in NZW rabbits. To investigate the veracity of the above finding on cardiac cycle (CC) phases and elucidate the underlying mechanism we employ the HL-1 cell line of mouse atrial cardiomyocytes. Materials and methods
Confluent beating HL-1 cells were stained with 68 μM di-8-ANEPS in 68 μM Phoronic Pl-127. Cell beating and the accompanied fluorescent intensity changes, were recorded with a specialized high frequency sampling (1 kHz) CMOS camera (NeuroCMOS-SI128i, Redshit Imaging, Inc., USA) coupled to a fluorescent microscope (AxiolExaminer Z1, Carl Zeiss Microimaging GmbH, Germany). 15 optical recordings, of 2 s duration, were taken 1 min apart. 50 μM Aldo in Claycomb’s medium was added between the third and fourth recording (control received only the same volume of medium). CC total duration, contraction period (corresponding to cardiac systole) as well as relaxation period and duration of the ‘quite’ state of the cells (both corresponding to cardiac diastole) were calculated. Results
Our results show that Aldo increases the total duration of the CC (P<0.001 (Z-score (standard score) and Spearman’s r) almost immediately after its addition to the cells lasting up to 14 min, when recordings were stopped. This increase is attributed to the ‘quite’ state of the cells corresponding to the diastolic phase of the CC.

Conclusion
Aldo causes a reduction of the beating frequency of the HL-1 cells. Their prompt response to Aldo denotes a non-genomic action. Taking into account of our previous finding, this action can be attributed to elongation of the first part of cardiac diastole (protodiastole).

Disclosure
This work was supported by the Aristotle University of Thessaloniki Research Committee (grant number 89791).

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Ghrelin and GHSCR1 receptor in placenta of SGA, LGA, and AGA newborns
Martha I Gonzalez Dominguez1, Maria Luisa Lazo de la Vega Monroy1, Silvio Zaina1, Myrna Sabanero2, Leony Daza Benitez1, Juan Manuel Malacar1 & Gloria Barbosa Sabanero1
1Health Sciences Division, Medical Sciences Department, University of Guanajuato, Leon, Guanajuato, Mexico; 2Natural and Exact Sciences Division, Biology Department, Guanajuato University, Guanajuato, Guanajuato, Mexico; 3UMAE No. 48 IMSS, Leon, Guanajuato, Mexico.

INTRODUCTION
Intrauterine growth is a biological process regulated by maternal, placental, and foetal endocrine signals. Birth weight is an indicator of the health of the newborn. Alterations in foetal growth lead to perinatal health risks and favour metabolic diseases during adult life. Therefore, the study of endocrine factors determining birth weight, such as ghrelin, is an important issue. Ghrelin may exist as two molecular forms, desacyl ghrelin (DAG) and acyl ghrelin (AG). Current evidence showed that DAG as an active hormone with effects on different tissues in diverse physiological and pathophysiological states. Although cord blood (CB) ghrelin levels have been correlated to birth weight, it is unknown which ghrelin’s molecular variants are involved and if expression and methylation of ghrelin receptor (GHSCR1) has a role in foetal development.

METHODS
We performed a cross-sectional comparative study healthy mothers and their term newborns small for gestational age (SGA), adequate for gestational age (AGA), and large for gestational age (LGA) (n=20/group). Total ghrelin, AG, and DAG levels were measured in CB by ELISA. Placental GHSCR1 expression was evaluated by western blot and GHSCR1 promoter methylation by qPCR after bisulphite modification of DNA.

RESULTS
Cord blood DAG levels were increased in SGA compared to AGA newborns (902.1±109.1 and 597.4±58.2 pg/ml respectively, P=0.01) while LGA and AGA showed similar values (627.2±76.4 pg/ml for LGA, P=0.80). DAG levels negatively correlated with birth weight (r=-0.31, P=0.02) and placental weight (r=-0.37, P=0.01). No differences in AG or total ghrelin levels were found. Expression and methylation of GHSCR1 in placenta was not differentially among SGA, AGA, and LGA.

CONCLUSIONS
Our results showed that expression and methylation of ghrelin receptor (GHSCR1) has unrelateed with birth weight. Suggesting that additional factors, such as DAG, are involved in the mechanism that determines birth weight.

Disclosure
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Reproduction: Female and PCOS
GP.06.01
Habitual physical activity is associated with lower prevalence of insulin resistance in women with polycystic ovary syndrome
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Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting 7–18% of women of reproductive age, according to different criteria. Metabolic disturbances related to PCOS include dyslipidemia, obesity, and insulin resistance (IR) and women with PCOS have higher prevalence of impaired glucose tolerance and type 2 diabetes mellitus in comparison with weight-matched women without the syndrome. Evidence indicates that regular practice of physical activity improves insulin resistance in general population. Habitual physical activity is defined as any form of body movement with energy expenditure above resting levels, including work, leisure activities, and household chores. The aim of this study was to evaluate whether habitual physical activity is associated with less insulin resistance in women with PCOS. One hundred and four participants, 61 PCOS, by the Rotterdam criteria, and 43 control women, were stratified according to physical activity status: inactive (<7500 steps/day) or active (≥7500 steps/day). Habitual physical activity was assessed by counting the number of daily steps, using a digital pedometer. Anthropometric, clinical, and laboratory examination were also determined. The age of participants was 23.9±6.4 years old and most of them were Caucasians. While BMI was higher in PCOS than in controls, it was similar between active and inactive participants of each group. Hemoglobin A1c (HbA1c) levels and HOMA-IR were higher and sex hormone-binding globulin was lower in PCOS compared to controls (P<0.05). Abnormal fasting insulin (≥20 μU/ml) was found to be less frequent in active than in inactive PCOS (21.7 and 52.2%, P=0.009) as well as HOMA-IR ≥2.7 (34.0 and 44.7%, P=0.005) and lipid accumulation index (LAP) ≥34.5 (35.7 and 50%, P=0.013). Active vs inactive controls also presented similar results (P<0.05). In conclusion, habitual physical activity, specifically walking 7500 or more steps daily, was associated with lower frequency of insulin resistance, assessed by different clinical markers in PCOS women. These data suggest that even a slight to moderate non-structured daily physical activity might bring health benefits in PCOS before metabolic comorbidities become evident.

Disclosure
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Early diagnostics of insulin resistance in obese pregnant women
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AIM
To find early diagnostic criteria for metabolic syndrome (MS) in obese women in early pregnancy.

MATERIALS AND METHODS
We examined 143 pregnant women aged from 19 to 43 years (31.0 (26.0; 35.0)) and divided them into three groups: MS group (n=55), risk group (one to two components of MS) (n=57), and control group (n=31). Laboratory examination included blood pressure (BP), monitoring, assessment of a lipid profile, glucose metabolism, and insulin resistance (HOMA-IR).

RESULTS
76% of pregnant women with MS and 45% of pregnant women with one to two components of MS have obesity. Hypertension was diagnosed in 54 (64%) pregnant women. We found significant differences in systolic, diastolic, and pulse pressure between pregnant women with obesity and pregnant women without obesity (P<0.001). There were significant differences in level of fasting glucose, insulin and HOMA-IR, triglycerides, LDL-C, and VLDL-C in pregnant women with obesity comparing with pregnant women without obesity (P<0.001). Gestational diabetes (GD) was identified in the MS group up to 20 weeks in 18.2% of pregnant women, after 20 weeks in 29.1% of pregnant women. There were 10.5% of women with GD up to 20 weeks and 17.5% after 20 weeks in the risk group respectively. We found no disturbances in carbohydrate metabolism in 45.5% pregnant women from MS group and 71.9% from risk group.

CONCLUSION
Insulin resistance and its associated disorders of carbohydrate and lipid metabolism are common in obese women during pregnancy. Early identification of risk factors in obese pregnant women is a prerequisite for the prevention of serious complications in the future as part of the mother and the foetus.

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Characteristics of lipid profile in different phenotypes of polycystic ovary syndrome
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Introduction
Dyslipidaemia is a common metabolic derangement in polycystic ovary syndrome (PCOS) and may be represented with different lipid alterations. The aim of this study was to evaluate lipid profile in different PCOS phenotypes.

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Methods
We evaluated 365 PCOS women (PCOS: 25.05 ± 6.24 kg/m²; 25.48 ± 5.21 years) diagnosed using ESHRE/ASRM criteria and 125 BMI-matched healthy women (controls: 25.41 ± 6.16 kg/m²; 30.35 ± 5.62 years). PCOS group was divided into four phenotypes: a (anovulation (ANOV), hyperandrogenism (HA), polycystic ovary morphology (PCOM)), B (ANOV, HA), C (HA, PCOM) and D (ANOV, PCOM). Phenotype D had lower BMI in comparison to all other phenotypes (P < 0.05). Blood samples were collected during follicular phase of menstrual cycle for determination of total cholesterol (TC), LDL, HDL, triglycerides, apolipoprotein-A1 and apolipoprotein-B. Ratios TC/HDL, apolipoprotein-B/apolipoprotein-A1 were calculated.

Results
PCOS women in comparison to controls had higher levels of TC (5.07 ± 1.89 vs 4.89 ± 0.97 mmol/L, P < 0.001), LDL (3.16 ± 0.97 vs 3.09 ± 0.82 mmol/L, P = 0.002), TG (1.20 ± 0.85 vs 0.98 ± 0.54 mmol/L, P < 0.001), apolipoprotein-B (0.82 ± 0.29 vs 0.83 ± 0.25, P = 0.021), while there were no differences in HDL, apolipoprotein-A1 (P = 0.05). PCOS women had higher ratios: TC/HDL (3.94 ± 1.36 vs 3.68 ± 1.03, P = 0.001), LDL/HDL (2.46 ± 1.07 vs 2.36 ± 0.89, P = 0.019), TG/HDL (1.02 ± 1.20 vs 0.78 ± 0.61, P = 0.001), apolipoprotein-B/apolipoprotein-A1 (0.59 ± 0.33 vs 0.52 ± 0.19, P = 0.011). Comparisons between PCOS phenotypes revealed that phenotype D had lower levels of triglycerides and the ratio TG/HDL than other three phenotypes (P = 0.05 for all comparisons), while there was no difference in other lipid concentrations and ratios. Phenotype A, B and C had higher TC, TG, TC/HDL, TG/HDL, and apolipoprotein-B/apolipoprotein-A1 in comparison with controls, while there were no differences between phenotype D and controls.

Conclusion
In our group of women with PCOS, only phenotype D was characterised with less deteriorated lipid profile than other PCOS phenotypes.

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GP.06.04
Phenotypic characteristic of type 1 diabetic women with polycystic ovary syndrome
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Introduction
The prevalence of polycystic ovary syndrome (PCOS) is increased in women with type 1 diabetes (T1DM) in comparison to the general population. It has been suggested that exogenous insulin administered to T1DM women in supraphysiological doses could act as co- gonadotropin and lead to disturbances observed in PCOS.

Aim
The aim of this study was to evaluate the phenotypic characteristic and differences between diabetic women with PCOS (T1DM+PCOS) and age-, BMI-matched women with type 1 diabetes without PCOS (T1DM-no PCOS) and non-diabetic women with PCOS (PCOS).

Study participants and methods
We studied 108 women: 39 with T1DM (18 with T1DM+PCOS and 21 with T1DM-no PCOS), 47 with PCOS and 22 healthy women. PCOS was diagnosed using the Rotterdam criteria. The anthropometric measurements, clinical parameters, estimation of plasma concentrations of sex hormones, SHBG, HbA1c and ultrasonographic evaluation of the ovaries were performed for all women. In both diabetic groups insulin sensitivity was calculated with estimated glucose disposal rate (eGDR).

Results
There were no significant differences in anthropometric measurements between all studied groups. The Ferriman–Gallwey score was higher in women with PCOS than in those with PCOS+T1DM (P = 0.074). Hormonal profile was similar in both groups with PCOS. We observed that ovarian volume and ovarian follicle count did not differ in patients with PCOS+T1DM and PCOS. The number of ovarian follicles was higher in the PCOS+T1DM and PCOS groups versus the control (P = 0.008, P < 0.001) and versus the T1DM-no-PCOS group (P < 0.001, P < 0.001, respectively). HbA1c, daily insulin dose, eGDR were not different between PCOS+T1DM and T1DM-no PCOS. A significant negative relationship of eGDR with body fat mass and BMI was found in T1DM+PCOS (r = -0.75, P < 0.001, r = -0.75, P < 0.001), which was not observed in patients with T1DM-no PCOS.

Conclusion
We conclude, that phenotypic characteristic of T1DM+PCOS women is similar to PCOS. Further study are required to better understand the pathogenesis of PCOS in type 1 diabetic women.

Disclosure
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GP.06.05
Cytokine expression in SAT and VAT from PCOS patients and control women: possible proinflammatory effect of testosterone depending on BMI – a preliminary report
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Context
Insulin resistance is an important component of polycystic ovary syndrome (PCOS). Local cytokine production in adipose tissue increases local insulin resistance. The effect of testosterone on local adipose tissue cytokine production has not been explored thoroughly.

Aim
To evaluate cytokine expression in subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) from PCOS and control women and evaluate the response to testosterone on the later.

Methodology
We obtained serum samples and SAT by biopsy from ten PCOS and seven control women. In six different women (three PCOS and three controls) subjected to abdominal surgery we obtained samples from omental VAT that were incubated (300 mg each well) for 72 h in basal conditions or stimulated with 10⁻⁴ M testosterone (T). Expression of cytokines [IL1b, CCL-2, TNF-alpha and IL-6] in tissue samples was assessed by Real Time PCR. All women studied were 18–40 years old.

Results
Basal SAT and VAT cytokine expression and serum cytokine levels showed no differences between PCOS and control patients. Regarding stimulated tissue samples, there was no significant response to T in the total group or analysing PCOS or control patients independently. Nevertheless, in VAT samples from patients with a BMI between 30 and 40, testosterone seems to have a proinflammatory effect in VAT. Thus, the effects of testosterone in terms of cytokine expression might be influenced by the presence of obesity.

Disclosure
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**GP.06.06**  
**Does finasteride, as well as metformin, improve insulin resistance in PCOS?**  
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Introduction  
The effects of finasteride on insulin resistance and of metformin on hyperandrogenism in patients with polycystic ovary syndrome (PCOS) are not clear. This study therefore compared the effects of finasteride, metformin, and finasteride plus metformin treatments on hormone levels, insulin resistance, and hirsutism score in women with PCOS.

Subjects and method  
Fifty-two patients with PCOS were randomly assigned to receive finasteride 5 mg/day, metformin 1700 mg/day or finasteride plus metformin for 12 months. BMI, Ferriman-Gallway score (FGS), serum concentrations of estradiol, sex hormone-binding globulin, free testosterone, DHEAS, androstenedione, and HOMA-IR index and areas under the curve (AUC) for insulin and glucose were evaluated before and after 12 months of treatment.

Results  
Reductions in FGS, free testosterone, DHEAS, androstenedione, HOMA-IR, AUC-insulin, and AUC-glucose were significant within each group, whereas BMI and estradiol did not. Comparisons of changes in parameters in the three groups did not clearly show the superiority of any treatment modality.  

Discussion  
Insulin resistance and hyperandrogenism are the two major interacting pathophysiologial derangements in PCOS. Thus, treatment with finasteride alone should significantly reduce both androgen levels and parameters of insulin resistance; and our results confirmed that suggestion. In addition, metformin alone was effective, and not inferior to finasteride, in the treatment of hyperandrogenism.

Conclusion  
The finasteride, metformin, and their combination therapies were effective and safe in women with PCOS; since both drug classes have beneficial effects on both hyperandrogenism and insulin resistance.

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**GP.06.07**  
**The effect of metformin and liraglutide on markers of subclinical atherosclerosis in women with polycystic ovary syndrome**  
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Subclinical atherosclerosis is frequently present in women with polycystic ovary syndrome (PCOS). Metformin and liraglutide both improve metabolic control in PCOS, however they might exert different anti-atherosclerotic effects. We investigated the impact of these medications on the subclinical atherosclerotic changes of the arterial wall in PCOS patients.

Methods  
72 women with PCOS (aged 28.6±6.3 years, BMI 38.4±5.0 kg/m², mean ± s.d.) were assigned to therapy with either metformin 1 g BID or liraglutide 1.2 mg QD sc. for 12 weeks. Markers of subclinical atherosclerosis including intima-media thickness (IMT), flow-mediated dilation (FMD), low-flow-mediated constriction (L-FMC), and peripheral tonometry (PAT) with pulse wave amplitude (PWA) were measured. Arterial stiffness was investigated through pulse wave velocity (PWV) and the augmentation index (AI). All measurements were obtained at baseline and at study end.

Results  
25 patients on metformin and 40 patients on liraglutide completed the study. Metformin improved FMD from 7.33±3.11 to 9.12±2.75% (P = 0.04). Liraglutide decreased IMT from 0.53±0.06 to 0.50±0.05 mm (P = 0.04), arterial stiffness as assessed by AI from 31.4±7.8 to 39.6±13.1 (P = 0.03) and also caused a border-line, non-significant improvement of PWA (P = 0.07). Furthermore, there was a significant inverse relationship between FMD and HOMA index before and after treatment in both arms (r = 0.61, P < 0.05).

Conclusions  
Short-term intervention with metformin and liraglutide have beneficial effect on markers of subclinical atherosclerosis in obese women with PCOS. Interestingly, the effects of metformin therapy resulted only in functional improvement, whereas liraglutide also ameliorated morphological signs of atherogenesis of the arterial wall.

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**GP.06.08**  
**Plasma brain derived neurotrophic factor is decreased in women with polycystic ovary syndrome and related to the markers of endothelial dysfunction**  
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Introduction  
Brain derived neurotrophic factor (BDNF) is a neurotrophin which plays a role in neuronal growth and differentiation. Decreased level of BDNF is supposed to play a role in the pathogenesis of the neurodegenerative diseases. Recent data indicate that BDNF could be also involved in angiogenesis. Several lines of evidence support the role of BDNF in glucose metabolism. The decreased level of BDNF are observed in obesity and type 2 diabetes mellitus. Polycystic ovary syndrome (PCOS) is a common endocrine disorder associated with insulin resistance and increased risk of cardiovascular diseases. The aim of the present study was to determine plasma BDNF concentration in patients with PCOS in comparison to healthy women.

Study participants and methods  
We studied 74 women with PCOS (BMI = 27.6±6.73 kg/m²) and 37 healthy, regularly menstruating women (BMI = 26.69±6.72 kg/m²). PCOS was diagnosed with Rotterdam criteria. Clinical examination, anthropometric measurements, hyperinsulinaemic, euglycaemic clamp and estimation of plasma concentrations of BDNF, sex hormone binding globulin (SHBG), adiponectin, soluble E-selectin (sE-selectin), intercellular adhesion cell molecule-1 (sICAM-1), hormonal and lipid profile were performed in all study participants.

Results  
Women with PCOS had significantly higher LH (P < 0.0001) and FSH (P = 0.04) in comparison to the control group. Plasma BDNF concentration was lower in PCOS group vs controls (P = 0.04). Subgroups analysis revealed that plasma BDNF was significantly lower in the obese PCOS women vs obese controls (P = 0.03), whereas such difference was not found between lean PCOS and control women. In PCOS group, plasma BDNF correlated significantly with SHBG (r = 0.26, P = 0.02), adiponectin (r = 0.29, P = 0.012), sICAM-1 (r = -0.28, P = 0.014) and sE-selectin (r = -0.24, P = 0.03), which was not observed in the control group.

Conclusion  
Our data indicate that BDNF is decreased in obese PCOS women and related to the markers of endothelial dysfunction.

Disclosure  
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Reproduction: Female and other

GP.07.01

Preconceptional TSH and miscarriage in infertile women submitted to IVF

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It is known that high levels of TSH are associated with higher miscarriage risk, though the precise TSH cut-offs are debated. Aim of the present study was to evaluate if pre-conceptional TSH levels associate with increased risk of early miscarriage in a large series of infertile women submitted to IVF and to determine the threshold of TSH associated with the highest prevalence of pregnancy loss. We retrospectively studied 1484 infertile women (mean±S.D. BMI 22.7±4) submitted to IVF in a single center from 2004 to 2014. Overall, 371/1484 (25%) patients had a biochemical pregnancy and 152 patients experienced a pregnancy loss. Mean TSH levels of women with a regular pregnancy were significantly lower than mean TSH levels recorded in patients with a pregnancy loss (1.8±0.8 vs 2.2±1.5. P=0.01). Interestingly, the miscarriage rate was progressively higher for increasing TSH cut-off levels (≤2.5 vs >2.5 P=0.08; ≤3 vs >3 P=0.001; ≤4.5 vs ≥4.5 P=0.004). Moreover, among the 152 women with pregnancy loss 59 (39%) were clinically pregnant and had a miscarriage in the first trimester, while in 93 patients (61%) a biochemical pregnancy without clinical evolution was documented, but no significant differences in mean TSH levels were recorded between women with different time of miscarriage. In conclusion, in women undergoing IVF, lower TSH levels reduce the risk of early pregnancy loss. These data strongly indicate the need for TSH screening prior to IVF procedures, and suggest the treatment of women with TSH levels >3 mU/L.

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GP.07.02

Kisspeptin increased during reproductive ageing and is regulated by sympathetic nerve system

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Kisspeptin is found in the ovary of different species including human and rat. We have recently described, through in vitro studies, that kisspeptin is under the control of sympathetic innervation of the ovary. Considering that ovarian activity of sympathetic nerves increases with ageing, it is possible that the ovarian kisspeptin also increases during this period. As a role of kisspeptin in folliculogenesis has been postulated, this increase in kisspeptin could participate in the changes in follicular dynamics that occur during the subfertility period. We conducted an in vivo study to determine if the ovarian sympathetic tone participates in kisspeptin expression during reproductive ageing. To achieve this, we measured kisspeptin mRNA and protein levels by qRT-PCR and western-blot at 6, 8, 10 and 12 months old rats, covering the ageing. To achieve this, we measured kisspeptin mRNA and protein levels by qRT-PCR and western-blot at 6, 8, 10 and 12 months old rats, covering the ageing. To achieve this, we measured kisspeptin mRNA and protein levels by qRT-PCR and western-blot at 6, 8, 10 and 12 months old rats, covering the ageing. To achieve this, we measured kisspeptin mRNA and protein levels by qRT-PCR and western-blot at 6, 8, 10 and 12 months old rats, covering

GP.07.03

The role of transvaginal ultrasonography in the evaluation of endometrial hyperplasia or cancer in pre- and perimenopausal women

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Objective
The aim of our study is to determine clinical factors and sonographic findings associated with endometrial hyperplasia or cancer (EH+) in pre- and perimenopausal women.

Study design
A total of 14,340 transvaginal ultrasonography examinations of 9,878 healthy pre- and perimenopausal women were included in this retrospective study. One hundred sixty-two subjects underwent endometrial biopsy based on abnormal uterine bleeding (AUB), sonographic endometrial abnormalities (thickened endometrium, endometrial mass, or endometrial stripe abnormality), or both. The clinical factors and sonographic endometrial abnormalities were evaluated with regard to EH+.

Results
Histologically verified EH+ was found in fourteen subjects (8.6%); ten cases of endometrial hyperplasia without atypia (EH), three cases of endometrial hyperplasia with atypia (AEH), and one case of endometrial cancer. Neither clinical factors nor AUB were associated with EH+ (P=0.003) and marginally associated with AEH+ (P=0.06). However, simple measurement of endometrial thickness has a limited role in this capacity.

Conclusions
Endometrial stripe abnormality is a significant factor to predict EH+ in healthy pre- and perimenopausal women with and without AUB. However, simple measurement of endometrial thickness has a limited role in this capacity.

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GP.07.04

Expression of melanocortin receptors in human endometrium

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Background
The melanocortin system is known to be involved in hypothalamic regulation of energy balance, which is implicated in reproductive success. However, the peripheral role for melanocortin receptor (MCR) signalling in the reproductive system has not been described. During a clinical trial of repeated high dose tetracosactide (ACTH1-24) injection, four of nine premenopausal women with Addison’s disease developed menstrual disturbances. We wondered if these adverse effects were mediated via direct melanocortin signalling in human endometrium, which has not been previously examined.

Methods
Endometrial (n=8) biopsies were obtained from pre-menopausal women after hysterecomy for non-endometrial pathology. Decidual (8–10 weeks gestation; n=5) tissues were obtained after termination of apparently normal pregnancies.

The localisation of the expression of melanocortin receptors (MCR 1-5) in human endometrium was performed using immunocytochemistry. Tissue culture was used to characterize the effects of ACTH1-24 on decidual tissue and blood vessel integrity determined by immunostaining for vascular smooth muscle cell (VSMC) markers.
Results
Robust expression of MC5R was demonstrated in human endometrium. Moderate to strong MC2R and MC3R expressions were also shown in this tissue. Expression of MC1R and MC4R was negligible. A dose-dependent reduction in VSMC in the cultured decidual tissue’s vessel wall was observed during treatment with high concentrations of ACTH$_{1-24}$. However, the difference was only significant after treatment with the highest concentration of ACTH (500 ng/ml) (P<0.03).

Conclusion
Our study demonstrated for the first time MC2R, MC3R and MC5R expression in human endometrium at the protein level. These melanocortin receptors may play a role in regulating endometrial proliferation or integrity, which could mediate menstrual disturbances observed in the clinical trial. Understanding of melanocortin receptors’ role in the uterus and decidual tissue could potentially inform the pathogenesis of uterine dysfunction. The effects of ACTH excess or deficiency on the endometrium via melanocortin signalling should also be explored further.

Disclosure

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**GP.07.05**

mRNA expressions of skin steroidogenic enzymes in women with idiopathic hirsutism

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Introduction
The pathogenesis of idiopathic hirsutism (IH) is not clear. On the other hand, human skin possesses all the enzymes necessary for androgen synthesis and catabolism indicating that it is an independent peripheral endocrine organ. Thus, in the present study we aimed to investigate the mRNA expression of aromatase enzyme and the other enzymes having functional roles in the steroidogenic pathway, in freshly obtained skin tissue from subumblical region and the arm of women with IH.

Patients
We aimed to determine mRNA expressions of genes associated with local androgen synthesis and metabolism (CYP11A1, STS, CYP19A1, SRD5A1, SRD5A2, HSD3B1, AR, COMT, ESR1, ESR2, HSD3B2, CYP17A1, SULT2A1, SULT1E1, HSD17B2, IL6, TGFβ1, TNF-α) from skin biopsy and blood samples of 21 patients with IH and the data compared with 15 healthy women.

Results
We found that patients with IH exhibit significantly lower expression of IL-6 mRNA and higher steroid sulphatase (STS) and HSD17B2 gene mRNA expression, respectively, in the subumblical region skin biopsies. Similarly, patients with IH exhibit significantly lower IL-6 mRNA expression and higher STS and HSD17B2 gene mRNA expression, respectively, in the arm skin compared to healthy women’s subumblical region. There were no significant differences in any gene expression between the arm and subumblical skin biopsies in the patient group. In addition, there were no significant differences in any gene expression in peripheral blood mononuclear cells of the patients and healthy women.

Discussion
Our results suggest that the increased mRNA expression of HSD17B2 and STS genes, decreased IL-6 mRNA are not dependent on circulating levels of testosterone. In both arm and umbilical skin biopsy of patients with idiopathic hirsutism, we observed an up-regulation of HSD17B2 and STS, decreased IL-6, probably determining an increase in the local amount of active androgens, which could then be used as substrate for other androgen metabolic routes.

Disclosure
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**GP.07.06**

Difficulties in the evaluation of hirsutism using the modified Ferriman-Gallwey scale

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Inconsistencies in hirsutism evaluation using The Modified Ferriman-Gallwey scale (mFG) between different evaluators and need for hirsutism diagnostics standardization has been reported in numerous publications.

Materials and methods
The study was conducted during the period March to June of 2013. The study was carried out by six physicians – one specialist in female hyperandrogenism (an expert physician), and five – with no such experience. At the beginning of the study, the expert physician trained other researchers in the evaluation of terminal hair growth using mFG scale. The study included 90 women who presented to the endocrinologist’s consultation due to different reasons except hyperandrogenism and met the inclusion criteria. The subjects underwent anthropometric measurements, and were asked to perform self-evaluation of hirsutism according to the mFG scoring method. Following that, hirsutism was evaluated by the physicians-researchers using the same mFG scoring method.

Results
The study included healthy 20–34 year old (mean age 25.2 years, 95% CI 23.8–26.5) women with regular menstrual cycles. The total mean score of the subjects’ self-evaluation was 7.0, 95% CI 4.6–9.3. The total mean score of the evaluation given by the researchers was 2.81, 95% CI 1.5–4.2. The odds ratio for erroneous evaluation of hirsutism on the upper lip was 1.31 (95% CI 1.02–1.69), on the lower abdomen and the thigh – 5.44 (95% CI 4.23–7.02), and on the chest – 0.20 (95% CI 0.02–0.04).

Conclusions
A discrepancy was found between the evaluations submitted by the expert physician and one of evaluators, whereas the differences between the evaluations presented by the other researchers were not significant. The women who participated in the study significantly more frequently submitted higher mFG scores when evaluating their hirsutism than the researchers did. The greatest differences between the evaluations of hirsutism were found on the upper lip, the lower abdomen, and thighs. Extensive training is needed before starting use The Modified Ferriman-Gallwey scale in order to get reliable results of hirsutism evaluation.

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**GP.07.07**

Incretin release in a different state of testosterone level among lean PCOS women – case control study

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Introduction
Incretins are peptide hormones, responsible for 70% of the insulin release after oral glucose intake. An impaired incretins secretion was noted in several conditions involving insulin resistance, including polycystic ovary syndrome
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Reproduction: Male and endocrine disruptors

GP.08.01

Characteristics and predictors of primary hypogonadism in ageing men: longitudinal data from the European Male Ageing Study

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Introduction

Primary hypogonadism (PHG, testosterone <10.5 nmol/l and LH >9.5 U/l) without a recognisable cause affects ~2% of community-dwelling middle-aged and older men. We sought to identify the clinical significance of, and risk factors for, this apparently age-related hypogonadal state.

Methods/design

The European Male Ageing Study (EMAS) is a prospective observational cohort survey of 3,369 community-dwelling men aged 40–70 in eight European countries who underwent follow-up assessment an average of 4.3 years later. Men were classified as incident if PHG (Eugonadal (EUG) at baseline, PHG at follow-up) or persistent (p) PHG (PHG at baseline and at follow-up), Differences in clinical and laboratory parameters between the groups and potential risk factors for iPHG were assessed using descriptive statistics and regression models.

Results

Of the 1,996 men comprising the analytical sample, 1,946 (97.5%) had pEUG, 23 (1.15%) had iPHG, 22 (1.10%) pPHG, and 5 (0.25%) reverted to EUG. The incidence of PHG was 0.27%/year. At baseline, iPHG (compared to pEUG) men were on average 9 years older (P=0.001), more likely to be smokers (OR 5.9 (1.8–18.6); P=0.003) and tended to have more illnesses (OR 2.8 (0.9–8.5); P=0.069). Their baseline total and free T levels were lower, and gonadotropin levels higher than in pEUG men. Upon transition from EUG to PHG, the characteristics which worsened significantly included erectile dysfunction, walking limitation, haemoglobin, self-rated physical function and frequency of >2 illnesses. Clinical parameters in iPHG and pPHG at follow-up were in the main similar.

Conclusion

PHG is a relatively rare condition in ageing men. The major risk factors for its development include older age, smoking and chronic illness. PHG in ageing men is characterised by clinical features compatible with both androgen deficiency and deteriorating functional health.

Disclosure

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GP.08.02

Deregulation of Sertoli and Leydig cells function in patients with Klinefelter syndrome as evidenced by tests transcriptome analysis

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Background

Klinefelter syndrome (KS) is the most common abnormality of sex chromosomes (47,XXY) and represents the first genetic cause of male infertility. Mechanisms leading to KS testis degeneration are still not completely defined but considered to be mainly the result of germ cells loss. In order to unravel the molecular basis of global testis dysfunction in KS patients, we performed a transcriptome analysis on testis biopsies obtained from six azospermic non-mosaic KS patients and three control subjects.

Results

The analysis found that, compared to controls, KS patients showed the differential up- and down-expression of 656 and 247 transcripts. The large majority of the deregulated transcripts were expressed by Sertoli cells (SCs) and Leydig cells (LCs). Functional analysis of the deregulated transcripts indicated changes of genes involved in cell death, inflammatory response, lipid metabolism, steroidogenesis, blood-testis-barrier (BTB) formation and maintenance, as well as spermatogenesis failure.

Conclusions

Taken together, the present data highlight the modulation of hundreds of genes in the somatic components the testis of KS patient. The increased LCs steroidogenic function together with the impairment of inflammatory pathways and BTB structure, result in increased apoptosis. These findings might represent a critical roadmap for therapeutic intervention and prevention of KS-related testis failure.

Disclosure

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GP.08.03
Infertile men have frequently Leydig cell dysfunction: study on hypogonadism, vitamin D and bone mass in 5177 subjects
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Spermatogenic disruption is normally recognized by low sperm count and FSH levels. However, Leydig cell impairment is also frequent in subjects with primary testicular damage, as evidenced for example by reduced INSL3 and 25(OH)-vitamin D levels. The latter is caused by reduced expression of CYP2R1, a major enzyme involved in 25-hydroxylation of cholecalciferol. Furthermore, testosterone (T) production by the Leydig cells might be also impaired in men with primary spermatogenic damage. To clarify these we evaluated the presence and type of hypogonadism, 25(OH)-vitamin D status and bone mass in a very large cohort of infertile males. Among subjects referred to our tertiary University Centre for semen analysis during the period January 2011 to June 2014 (11 516 semen analysis) we report here the data of men who completed the andrological program, including semen culture (n: 10 394), history and physical examination (n: 7527), hormone analysis (FSH, LH, T, 25(OH)-vitamin D; n: 5884), and ultrasound of the testes (n: 5177). Men with total sperm count <10 million ejaculate (n: 2583) underwent also genetic analysis (karyotype, Yq microdeletions, CFTR mutations; n: 2273) and DXA (n: 855). Azospermia was present in 9.3% of cases, oligozoospermia (with or without reduced motility and/or normal sperm morphology) in 40.6%, asthenozoospermia in 12.9%, and normal sperm count in 34.5. Men or risk factors were varicocele (28%), genetics (15%), obstruction/sub-obstruction of seminal tract (12%), cryptorchidism (6%), infections/astrogenic causes/ejaculation disorders/prior surgery (14%) and idiopathic forms (25%). Primary hypogonadism (T<10.4 nmol/l, LH>8 IU/l) was found in 25.7% of cases, secondary hypogonadism (T<10.4 nmol/l, LH<1.5 IU/l) in 1.3%, subclinical hypogonadism (T>10.4 nmol/l, LH>8 IU/l) in 34.2%. Men with all forms of hypogonadism have frequently insufficient (48.5%) or deficient (25.4%) 25(OH)-vitamin D levels and higher risk of low bone mass, osteoporosis (16.8%) and osteopenia (31.5%). This study showed that hypogonadism and low vitamin D levels are very frequent in infertile males. Both conditions are implicated in the frequent low bone mass seen in these patents. Metabolic and other clinical conditions associated with low T and low vitamin D levels need therefore to be accurately evaluated in these subjects, and treatment should consider also these aspects.

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GP.08.04
Triclosan-induced breast cancer growth was antagonised by kaempferol, a phytoestrogen, via regulating cell cycle, migration and apoptosis related genes in MCF-7 breast cancer cells
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Triclosan (TCS) is one of endocrine disrupting chemicals (EDCs) derived from toothpastes, deodorant and cleaning supplies. As a phytoestrogen, kaempferol (Kaem) is found at variety of vegetables. In this study, we examined anti-proliferative effects of Kaem in TCS-induced cell growth in MCF-7 breast cancer cells. In MTT assay, TCS (10⁻⁸ M) increased the cell viability of MCF-7 cells, while Kaem (50 μM) significantly reduced the cell viability compared to a control (0.1% DMSO). Kaem reversed TCS-induced MCF-7 cell growth at 50 μM. To confirm that Kaem inhibited TCS-induced cell growth, we examined the transcriptional levels of cell growth and apoptosis-related markers using reverse transcription (RT)-PCR. The expression levels of cyclin D, cyclin E and were increased, while that of p21 and bax mRNAs was decreased by TCS in MCF-7 cells. In addition, Kaem treatment significantly reversed TCS-induced gene expressions. In parallel with its nuclear level, the protein level of cyclin E, cyclin D, cathepsin D, p-RRS1, p-AKT, p-ERK and p-MEK1/2 were induced by TCS while it was reversed by Kaem. The expression levels of p21 and bax genes was altered by TCS and reversed by Kaem treatment. For in vivo assay, a xenografted mouse model was generated following injection with MCF-7 breast cancer cells. In parallel with in vitro results, tumour volumes following treatment with E₂ and TCS were continually increased compared to a vehicle (corn oil). It was of interest that treatment of the mice with combination of E₂ plus Kaem or TCS plus Kaem showed less tumour formation rather than that of single treated mice with E₂ or TCS. Taken together, these results indicate that Kaem may inhibit the growth MCF-7 cells via regulating the expression of cell cycle, migration and apoptosis-related genes, suggesting that TCS-induced progression of breast cancer may be suppressed by a phytoestrogen (This work was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (MEST) of the Republic of Korea (2014R1A1A2055295)).

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GP.08.05
Involvement of oestrogen receptor-z in 17-cyhalothrin and cypermethrin-induced cancer growth in BG-1 ovarian cancer cells expressing oestrogen receptor
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Synthetic pyrethroids (SPs) are the most common pesticides which are recently used for indoor pest control. The widespread use of SPs has resulted in the increased exposure to wild animals and humans. Recently, some SPs are suspected as endocrine disrupting chemicals (EDCs) and have been assessed for their potential oestrogenicity by adopting various analyzing assays. In this study, we examined the estrogenic effects of 17-cyhalothrin (LCT) and cypermethrin (CP), the most commonly used pesticides in Korea, in BG-1 ovarian cancer cells expressing estrogen receptors (ERs). To evaluate the estrogenic activities of two SPs, LCT and CP, we performed MTT assay and reverse-transcription polymerase chain reaction (RT-PCR) for LCT or CP treated BG-1 ovarian cancer cells. In MTT assay, LCT (10⁻⁶ M) and CP (10⁻⁸ M) significantly induced the growth of BG-1 cancer cells in a dose-dependent manner. LCT or CP-induced cell growth was reversed by addition of 17β 20.720 (10⁻⁶ M), an ER antagonist, suggesting that this effect appears to be mediated by an ER-dependent manner. Moreover, RT-PCR results showed that transcriptional level of ERz was significantly down-regulated by LCT and CP. Taken together, these results indicate that LCT and CP may possess estrogenic potentials to stimulate the growth of ovarian cancer cells expressing ERs via an ER-dependent manner. Based on the observations from these in vitro results, we will examine in vivo oestrogenicity of LCT and CP in a xenografted mouse model transplanted with human BG-1 ovarian cancer cells (This work was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (MEST) (2013R1A1A2059092)).

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GP.08.06
Bisphenol A affects amelogenesis by modulating enamel key genes expression
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Bisphenol A (BPA) is a widespread endocrine disruptor commonly used by plastic industries. More than 95% of the world population contains BPA (ng/ml) in biological fluids raising the question of its activity and potential adverse effects. Anecdotally, molar incisor hypomineralisation (MIH), an
enamel pathology affecting 15–18% of children, is increasing concurrently with ED related pathologies. Our previous data show that BPA impacts amelogenesis and generate similar enamel defects as those described for MIH. The aim of the present study is to identify BPA target genes in order to characterize the mechanism of action of low-dose BPA in induced hypomineralisation. First, rats were exposed daily to 5 μg/kg per day BPA from the conception to the sacrifice. RNAs from microdissected dental epithelia were submitted to microarray analysis. Among the 19 239 tested RNAs, only 41 were modulated (more than 1.5-fold) by BPA. Interestingly, among these genes, amelogenin and enamelin coding for specific enamel matrix proteins were ones of the highly up-regulated. Four other genes involved in mineralization process, SLC5A8, SLC26A4, SLC44A4 and Carbonic Anhydrase VB also appeared as BPA target genes which expression modulation may explain enamel hypomineralisation. Second, in vitro analysis carried out on the rat ameloblastic HA1T7 cells also showed transcriptional modulations of enamel gene expression by 10⁻¹⁰ M BPA. Further studies are currently underway to decipher transcriptional modulations in relation with steroid receptors (ERz and AR) involved in BPA effects during amelogenesis. In conclusion, we report that BPA impacts enamel synthesis through modulations of enamel key gene expression. Despite the small number of BPA target genes specifically expressed in ameloblasts, ubiquitous receptors such as ERz and AR are involved in BPA effect transmission. Thus, these data help to understand how irreversible enamel defects may be used as early marker of exposure to BPA some years before the diagnosis of related heavy pathologies.

Disclosure
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GP.08.07
Cord blood insulin-like peptide 3 is reduced in idiopathic cryptorchidism and inversely related to free bisphenol A: a marker and/or an actor of foetal exposure to endocrine disruptors?
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Introduction
Cryptorchidism, the most frequent congenital malformation in full-term male newborns, increases risk of infertility and testicular cancer. Most cases remain idiopathic but epidemiological and experimental studies have suggested the role of both genetic and environmental factors. Physiological testicular descent is regulated by two major Leydig cell hormones: Insulin-like peptide 3 (INSL3) and testosterone.

Methods and results
From a prospective case control study, 52 idiopathic non syndromic, cryptorchid newborns were compared to 118 matched controls, all born after 34 weeks pregnancy. Cord blood (cb) INSL3 (modified validated enzyme-linked immune-sorbent assay) but not cb testosterone (ultrapressure liquid chromatography-tandem mass spectrometry) was decreased in unilateral idiopathic cryptorchidism (P = 0.03) especially in transient forms (P = 0.02) and in the subgroup of non-palpable testis compared to the subgroup of palpable testes (supra-scrotal, inguinal or high scrotal) according to Scorer classification (P = 0.01). cb free bisphenol A (BPA) (RIA validated by High Pressure Liquid Chromatography-tandem Mass Spectrometry) in cryptorchid boys was not significantly increased (P = 0.1). However, in the whole study population (cryptorchid and control), cb free BPA correlated negatively with INSL3 (P = 0.01; R² = 0.05) but not with testosterone.

Conclusion
INSL3, a major actor of foetal testicular descent, but not testosterone, is decreased at birth in idiopathic cryptorchidism. This hormonal decrease may have contributed earlier in foetal development, to the impaired testicular descent. The inverse correlation we found between cbINSL3 and cbBPA is strengthened by the paper reporting that INSL3 gene is negatively regulated by BPA in ex vitro cultivated foetal human testes. While measurements of cb BPA and cb INSL3 may not exactly reflect earlier foetal production or exposure, our results support the role of INSL3 as a marker and/or an actor of foetal exposure to endocrine disruptors such as BPA.

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GP.08.08
Evidence of stimulation of pubertal development and suppression of growth rate in boys smoking marijuana in cigarettes
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Evidence indicates that normal pattern of progression of puberty is altered under certain conditions of stress, whereas growth rate is affected by sustained higher concentrations of cortisol, a marker of stress reactivity. Available data show that early teens commonly resort to use of drugs. The use of drugs may evoke stress responses, which may alter pubertal development and affect growth rate. Body weight (BW), height, BMI and plasma concentrations of LH, testosterone (T), GH and cortisol were determined in non-smoking (n=220) and marijuana users (n=217) boys. Acute effect of marijuana on salivary concentrations of cortisol was assessed by giving 0.25 g of marijuana in cigarettes to ten drug addict volunteers and determining salivary cortisol concentrations 15 min before and after 15 and 30 min of smoking. Plasma concentrations of LH, T and cortisol at late puberty/adolescence in both groups. The plasma concentrations of LH, T and cortisol were significantly higher in the whole study population (cryptorchid and control), cb free BPA and cb INSL3 were negatively correlated (P = 0.01). cb INSL3 and cbBPA are interrelated (P = 0.02) especially in transient forms (P = 0.01). However, in the whole study population (cryptorchid and control), cb free BPA correlated negatively with INSL3 (P = 0.01; R² = 0.05) but not with testosterone.

Conclusion
INSL3, a major actor of foetal testicular descent, but not testosterone, is decreased at birth in idiopathic cryptorchidism. This hormonal decrease may have contributed earlier in foetal development, to the impaired testicular descent. The inverse correlation we found between cbINSL3 and cbBPA is strengthened by the paper reporting that INSL3 gene is negatively regulated by BPA in ex vitro cultivated foetal human testes. While measurements of cb BPA and cb INSL3 may not exactly reflect earlier foetal production or exposure, our results support the role of INSL3 as a marker and/or an actor of foetal exposure to endocrine disruptors such as BPA.

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Nuclear receptors and signalling

GP.09.01
Comparison of mRNA expression pattern of retinoid and retinoid X nuclear receptor subtypes in thyroid carcinomas, breast cancer and renal carcinomas
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Introduction
Nuclear retinoid receptors (RARs) upon a ligand binding act as all-trans retinoic acid-inducible transcription factors interacting as heterodimers with nuclear retinoid X (rexinoid) receptors (RXRs). The disruption of retinoic acid (RA) signalling pathways is believed to underlie the etiology of a number of malignancies. Retinoids – cell differentiation agents that may ‘reprogram’ tumours, i.e. retinoic acid derivatives or retinoic acid related compounds with reduced teratogenic and other side effects are still highly required. In this study, we have investigated expression pattern of retinoid receptor subtypes (RARz, RARα, RARγ) and retinoid X receptor subtypes (RXRα, RXRβ, RXRγ) in thyroid carcinomas, breast cancer and renal carcinomas.
three different organ malignancies, i) thyroid different carcinoma tissues, ii) breast cancer tissues, and iii) renal cancer tissues.

Description of methods/design

Approximately 40 samples of different types of thyroid carcinoma, more than 150 breast cancer samples, and over 100 samples of renal carcinoma have been analyzed. The expression pattern of the retinoid/retinoid nuclear receptor subtypes has been evaluated by the RT-PCR techniques.

Results

Significantly increased expression of RAR\text{a} and RAR\text{b} in overall group of papillary carcinoma patients was demonstrated. In breast cancer, the expression of respective RAR subtypes was in the following order: RAR\text{a} > RAR\text{b} > RAR\text{g}. Among RXR subtypes, only RXR\text{b} was significantly diminished in breast cancer tissue. In renal carcinomas, expression of RAR\text{b} and RAR\text{g} was higher when compared to intact kidney tissue. Expression of RAR\text{a} was found to be markedly decreased in all renal tumours. All renal tumours were capable to express RAR\text{a} and RAR\text{b}.

Expression of RAR\text{a} was significantly lower in comparison with intact renal tissue.

Conclusion

The molecular mechanisms demonstrating differences in RAR and RXR subtype mRNA expression patterns in thyroid carcinomas, breast and renal cancer may find exploitation in clinical oncology, predominantly, in the differential diagnosis of different organ neoplasms.

Disclosure

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**GP.09.02**

**Proliferative vs apoptotic signals in granulosa cells: β-arrestins as switch between life and death in vitro**

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Background

The immortalised human granulosa cell line (hGCL5) is not responding to gonadotropins, which fail to activate the cAMP/PKA/CREB pathway, progesterone production, cell rounding and apoptosis, suggesting that FSH- and LH/βCG-receptors (FSHR; LHCGR) are downregulated.

Aim

To investigate whether the mechanism of FSHR/LHCGR downregulation is associated with life/death signals in hGCL5 cells.

Methods

We evaluated the FSHR/LHCGR expression in cultured hGCL5 cells (0–15% serum) by real-time PCR and western blotting. The response to 50 nM FSH or 100 µM LH was evaluated by measuring cAMP and progesterone production by ELISA, as well as ERK1/2 and CREB phosphorylation by western blotting, cell viability by proliferation assay and confocal imaging, in the presence or absence of selective agonists/antagonists (i.e. the PKA inhibitor H-89, PMA as a PKC-ERK1/2 activator, sRNA against β-arrestin1/2).

Results

Despite the positive expression of FSHR/LHCGR in the presence of serum at both mRNA and protein level (linear regression; \( P < 0.05; n = 3 \)), FSH/LH stimulation was ineffective on cAMP/CREB activation and progesterone production (Mann-Whitney’s U-test; \( P > 0.05; n = 3 \)), suggesting uncoupling of the receptors to the Gs/α protein. Conversely, ERK1/2 phosphorylation was FSH/LH- and dose-dependent in the presence of serum, increasing cell proliferation within 3 days, an effect similar to that obtained by PMA (Mann-Whitney’s U-test; \( P < 0.05; n = 3 \)). β-arrestin1/2 sRNA transfection uncoupled the cAMP/PKA pathway, leading to cAMP/CREB activation and progesterone accumulation at high levels (Mann-Whitney’s U-test; \( P < 0.05; n = 3 \)), cell rounding, pro-caspar three cleavage and apoptosis. The pro-apoptotic effects of cAMP/PKA basal activation were augmented by FSH -but not LH- treatment and inhibited by H-89 selective PKA blockade. Accordingly, long-term (4–8 weeks) overexpression of FSHR resulted in high basal cAMP levels, cell rounding and apoptosis (Mann-Whitney’s U-test; \( P < 0.05; n = 3 \)), revealing the peculiar, dual role of FSHR in the activation of proliferative/apoptotic signals.

Conclusions

β-arrestins determine the FSHR-, rather than LHCGR-mediated signalling towards proliferative/apoptotic pathways, acting as selective switch between ERK or cAMP/PKA pathway activation.

Disclosure

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**GP.09.03**

**Agonist-selective phosphorylation of the human sst3 somatostatin receptor determined by phosphosite-specific antibodies**

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The human somatostatin receptor 3 (sst3) is expressed in about 50% of all neuroendocrine tumours. The sst3 receptor is unique among somatostatin receptors which can initiate apoptosis of tumour cells through activation of the tumour suppressor p53. Furthermore, treatment of the sst3 receptor with somatostatin or stable somatostatin analogues such as octreotide or pasireotide can inhibit tumour cell proliferation. However, little is known about the agonist-induced regulation of the human sst3 receptor. We have generated a series of phosphorylation-deficient mutants of the receptor and determined important sites for agonist-induced internalisation. Based on this information we generated phosphosite-specific antibodies for the carboxyl-terminal serine 337, threonine 341 and threonine 348, which enabled us to investigate the temporal patterns of sst3 phosphorylation and dephosphorylation. Here we demonstrate that pasireotide and octreotide were not able to promote a phosphorylation to the same extent as natural somatostatin. Similar the sst3-selective ligand L-796,779 did not promote any detectable phosphorylation or internalisation. We also show that sst3 phosphorylation occurred within minutes, whereas dephosphorylation and recycling of the sst3 receptor occurred at a considerably slower rate. We also identify G protein-coupled receptor kinases 2 and 3 (GRK2/3) and protein phosphatase 1 (PP1) as key regulators of sst3 phosphorylation and dephosphorylation.

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**GP.09.04**

**Characterisation of insulin and β3-adrenergic receptor heteromers: experimental and bioinformatics approach**

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Evidences for a functional link between insulin receptor (IR) and β3-adrenergic receptor (β3-AR) exist in the mouse heart and in retina and are correlated with the cardiovascular dysfunction under insulin-resistant states1 and a diabetic retinopathy phenotype2. In our recent study we showed that i) IR coexpression reduced β3-AR surface expression and accelerated its internalization, ii) provided evidence for direct interaction and higher-order β3-AR:IR oligomer formation, likely comprising heteromers of homodimers, and iii) identified prospective intracellular interaction domains engaged in heteromerisation3. In this study we examined the involvement of the cytoplasmic part of the IR β chain in heteromerisation and addressed the role of β3-AR:IR heteromer in signalling. Evidence suggesting that the cytoplasmic part of the IR β chain is prerequisite for the interaction with the β3-AR was provided by BRET2 saturation and Heteromer Identification Technology (HIT) assays using a IR 1–1271 mutant lacking the IR C-terminal tail region (amino acids from 1272 to 1360). In BRET2 saturation assays, IR 1–1271–Riuc8 mutant displayed lower BRET2 signal value and slightly reduced affinity compared to the WT IR. For the complex consisting of IR 1–1271–Riuc8:β3AR-GFP9 the saturation was not reached; most likely reflecting only random collisions. Furthermore, in the IR 1–1271–Riuc8:β3AR HIT assay with β-arrestin 2 no spontaneous agonist-induced increase in BRET2 signal was detected that would be indicative of β-arrestin 2 recruitment to the IR 1–1271–Riuc8:β3AR heteromer, arguing against ability of IR 1–1271 to heteromerise with the β3-AR. Additional in silico mutation analysis of IR predicted substitutions mostly affecting the binding to the β3-AR. β3-AR heteromerization also influenced the pharmacological phenotype of the β3-AR i.e. its ability to recruit β-arrestin 2 and cAMP signalling.

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are endothelial cells (ECs). During the stages of plaque instability/rupture, metalloproteinases (MMP2 and MMP9), their inhibitors (TIMP2 and TIMP1), RANK, RANKL, OPGL, MCP1, lysyl oxidase (LOX), PDGFB, and ADAMTS4 play critical role. We aimed to investigate i) the effect of oestrogens on the expression of the above molecules in ECs and ii) which type of estrogen receptor mediates these effects.

Methods
Human aortic endothelial cells (HAECs) were cultured, in the absence or in the presence of estradiol (E2) at various concentrations and for various incubation times without or with pre-incubation with TNFz (resembling a low grade inflammation state). The mRNA expression of all the aforementioned genes was assessed by real-time PCR. Zymography for MMP2 and MMP9 activity was also performed. The experiments were repeated in either ERα- or ERβ-transfected HAECs.

Results
HAECs did not express ERα and ERβ while they express G-protein coupled estrogen receptor 30 (GPR30). Incubation with E2 at low concentrations induced an increase in LOX and MCP1 mRNA expression. Zymography revealed that E2 induced a down regulation of active MMP2, dose-dependently. Incubation with E2 following pretreatment with TNFz induced a marginal increase in MMP9 and TIMP1 expression and a ten times increase in MCP1, dose-dependently. In ERα-transfected HAECs, incubation with E2 led to upregulation of TIMP1 and TIMP2 and in marginal increase of LOX and MCP1. E2 increased the expression of MCP1 and LOX while decreased the expression of PDGF in ERβ-transfected HAECs.

Conclusion
E2 induced different effects regarding atherogenic plaque instability through different ERs. The balance of expression of the various ER subtypes may play an important role in the paradoxical characterization of estrogens as both beneficial and harmful.

Disclosure
General Secretariat for Research and Technology.

References
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Calcium, Vitamin D and Bone

**GP.09.08**

Study of a possible interaction between reactive oxygen species and the mTORC1 pathway in the regulation of energy balance

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Obesity and its consequent metabolic disorders are severe health problems. The mechanistic target of rapamycin complex 1 (mTORC1) pathway is an important hypothalamic integrator of the actions of nutrients and hormones on food intake (FI). Nutrient availability also affects the formation of reactive oxygen species (ROS) in the hypothalamus and regulates neuronal activity. In the present study, we hypothesise that modulation of mTORC1 activity mediates ROS effects on FI. To this purpose, C57Bl6J mice or WT and KO mice deficient for the mTORC1 downstream target S6K1 were treated with an i.c.v. injection of the ROS producer H2O2 or the ROS scavenger honokiol, alone or in combination with the mTOR inhibitor rapamycin or the mTOR activator leptin and changes in FI and body weight were assessed. Western blots were performed to study hypothalamic mTORC1 activity, in the arcuate nucleus and increased ROS signal in POMC neurons. These effects were associated with a significant decrease in food intake over 24 h. Conversely, i.c.v. administration of honokiol increased FI. The behavioural effects of H2O2 and honokiol were not seen in S6K1 KO mice. Pharmacological experiments using i.c.v. coadministration of H2O2 and rapamycin in C57Bl6J mice showed that rapamycin (at a dose not acting on FI) was able to blunt the anorexigenic effect of H2O2. Similarly, i.c.v. honokiol administration combined with an i.p. leptin injection decreased the anorexigenic effect of leptin, suggesting that leptin requires ROS formation to reduce FI. Our preliminary results confirm that ROS modulators require a functional mTORC1 pathway to regulate FI. Studies are ongoing to better define this relationship at the molecular and neuroanatomical level.

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**GP.10.02**

Comparison of two methods in assessment of fracture risk of postmenopausal women with osteopenia

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Introduction

More than half of osteopoenic patients suffer from fracture (Fx), but BMD osteopenia is usually not considered for treatment indication. FRAX, tool that can identify patients with high Fx risk based on major risk factors, can be used as an interventional threshold. Past few years, trabecular bone score (TBS), the bone quality determinant, is a promising method identifying the high-risk patients according to degradation of trabecular bone.

Objective

Comparison of two methods, TBS and FRAX, in treatment consideration between postmenopausal women with osteopenia.

Methods

The group of osteopenic postmenopausal women were retrospectively analyzed. Using NOF cutoff values of 20% for major osteoporotic fracture and 3% for hip fracture were used to consider patients at high absolute 10 years risk of Fx. According to temporary consensus guidelines patients with BMD osteopenia + very low (degraded) TBS (<1.1) should be treated after secondary cause was excluded. TBS Insight tool was used to assess TBS derived from L-spine DXA scans.

Results

157 postmenopausal women (mean age 65.9 years, BMI 26.7 kg/m², T-score: neck = −1.2, L-spine 1.4, and TBS 1.24) were included. In total, by NOF cutoff 44 (28%) patients, who may be treated were identified. From that number 20 (12.7%) patients belonged to highly degraded TBS group. Another 32 (20.3%) patients with highly degraded TBS were identified in low risk FRAX group.

Conclusion

In the present study, the FRAX tool was able to identify additional 28% more patients in high fracture risk, which should be considered for treatment. From NOF high-risk group TBS identified 20 patients at increased risk of fracture and additional 32 patients from whole study group with degraded TBS who should be treated. According to this study, addition of TBS to FRAX brings novel info in identifying high Fx risk patients with osteopenia.

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**GP.10.03**

Local administration of non-diabetic MSCs to diabetic femoral fractures enhances callus remodelling and deposition of reparative bone

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Fractures in diabetic patients are slower to heal and have an increased risk for developing malunion as compared to non-diabetic individuals. Given the known deficiencies in diabetic progenitor cell number and differentiation capacity, it is reasonable to hypothesise the aetiology of diabetic fracture malunion is dysregulated progenitor function. Therefore, we investigated the therapeutic efficacy of locally administered non-diabetic human bone marrow derived mesenchymal stem cells (hMSCs) to support femoral fracture repair in a murine model of diabetes.

A dose escalation study was performed administering hMSCs directly to a femoral fracture in a murine model of diabetes. The effect of local hMSC administration on the diabetic condition was evaluated by weekly monitoring of mouse weight, blood glucose, and terminal levels of circulating HbA1c. No significant changes in body weight, blood glucose, or HbA1c as a result of hMSC administration was observed throughout the 56-day study. Animals maintained their weight at 26–28 g, their blood glucose levels >13 mM and HbA1c levels of 10–15% regardless of treatment group. MicroCT analysis indicates an increase in bone volume, a statistically significant increase in bone mineral density and trabecular thickness and a statistically significant decrease in the ratio of bone surface area to bone volume in animals treated with hMSCs as compared to saline treated controls. Further, four point bending analysis demonstrated a statistically significant increase in ultimate stress and e-modulus of the reparative bone. Although, the local administration of hMSCs did not alter the organismal diabetic condition, treatment of the diabetic fracture with hMSCs resulted in enhanced mechanical integrity of the neo reparative bone.
Therefore, the local administration of non-diabetic hMSCs to diabetic fractures has the potential to enhance callus remodelling resulting in the deposition of higher quality reparative bone.

Disclosure
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GP.10.04

Osteoporosis and osteopenia in patients after kidney and pancreas transplantation

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Background
Organ transplantation (Tx) is the standard treatment for end-stage renal failure in diabetic patients. With an improvement in patient and graft survival, the bone loss and persistent abnormalities in bone metabolism are long-term complications to manage.

Patients and methods
We investigated the prevalence of osteoporosis and osteopenia in 256 diabetic patients (142M, 114F) after the kidney and pancreas Tx for renal failure due to diabetic nephropathy. The bone loss was diagnosed with densitometry (DEXA) using Lunar Prodigy apparatus in years 2010–2014. The characteristics of bone metabolism were regularly examined and we measured on the plain CXR the clavicle bone index, which is the ratio of cortical bone width to total bone width at the midpoint of the shaft.

Results
Osteoporosis of lumbar spine (L spine) and/or hips was diagnosed in 53/256 patients (20%), osteopenia in 115/256 (52%) and 68/256 (28%) of patients had normal bone density. Patients with osteoporosis had affected mainly proximal femurs (hips) in 30/53 (94%) cases and distal forearm in 32/53 (60%). Osteoporosis of L spine was proven in 11/53 patients (21%) and osteopenia in 28/53 (53%) cases. Patients did not differ significantly in age, creatinine, calcium and parathormone (PTH) level. There was a tendency to lower BMD with years after the kidney and pancreas Tx (see Table). The bone index showed good correlation with the bone density measured by DEXA (P<0.01).

Conclusion
Diabetic patients after kidney and pancreas Tx have increased prevalence of osteopenia and osteoporosis (72%). Osteoporosis affects mainly the hips (94%) and distal forearm. Evaluation and managing of bone disease should be an integral part of pre- and after Tx medical care.

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GP.10.05

Effect of 1-year cross-sex hormonal treatment on bone mineral density of the lumbar spine in transgender patients

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Background
Oestrogen can increase bone mineral density (BMD) by decreasing bone turnover, which is mainly seen in trabecular bone. Testosterone can increase bone size, but the effect on BMD is less clear. Cross-sex hormonal treatment (CSHT) in transsexuals can therefore affect the BMD. For example, in male-to-female individuals (MFs) a lower BMD before start of CSHT has been described in comparison to healthy control men.

Objectives
To investigate the effects of CSHT on BMD during the first year of hormonal treatment in MFs and female-to-male individuals (FMIs).

Methods
Prospective study, part of European Network for Investigation of Gender Incongruence (ENIGI). 74 adult patients who completed 1 year of CSHT were included. In 37 FMIs and 37 MFIs a dual-energy X-ray absorptiometry (DXA) was performed to measure the BMD of the spine at start and after a year of CSHT.

In the FMIs received testosterone undecanoate i.m. (1000 mg/12 weeks), testosterone gel (50 mg/day), or testosterone esters i.m. (250 mg/2 weeks). The MF group was treated with estradiol valerate (2–4 mg/day) or an estradiol patch (200 μg/week) and most MFs received cyproteron acetate (50 mg/day) simultaneously.

Results
At baseline the BMD of the spine of the FMIs was 0.99 g/cm² (s.d. ±0.10) and after 1 year 1.00 g/cm² (s.d. ±0.10) reflecting a mean difference of 1% (95% CI −0.31 to 2.24). In the MFs at baseline and after 1 year, the BMD of the spine was 1.00 g/cm² (s.d. ±0.11) and 1.03 g/cm² (s.d. ±0.11) respectively, reflecting a mean difference of 3.6% (95% CI 2.30 to 4.86).

Conclusion
In FMIs the BMD of the spine remained stable after 1 year CSHT. In the MFs group, the BMD increased on average with 3%. Taken into account the short study period, the change in BMD suggests that BMD is an important variable in the follow up of transsexuals.

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GP.10.06

The (CAG)n repeat polymorphism of the androgen receptor gene is associated with bone mineral density in menopausal women

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Introduction
Osteoporosis is a systemic skeletal disease with a strong genetic component. The androgen receptor (AR) is encoded by the AR gene and mediates the action of androgens, which play an important role in bone metabolism. Polymorphisms in the AR gene may be implicated in the pathogenesis of osteoporosis.

Objectives
The present study aimed to explore the influence of the (CAG)n repeat polymorphism of AR gene on BMD and serum levels of osteoprotegerin (OPG), receptor activator of nuclear factor-κB ligand (RANKL), and bone metabolic markers in a Greek female population.

Methods
Two hundred and seventeen peri- and postmenopausal women aged 42–63 years were enrolled. All participants underwent spinal BMD evaluation by dual-energy X-ray absorptiometry (DXA). Genotyping of the (CAG)n repeat polymorphism was performed by PCR. Levels of OPG, soluble RANKL (sRANKL), and bone metabolic markers were measured.

Results
Genotype analysis revealed alleles having 15–30 CAG repeats. The (CAG)n polymorphism was significantly associated with spinal BMD. Women having biallelic mean CAG repeat number ≥21 had significantly lower spinal BMD (0.797±0.107 g/cm²) than women having biallelic mean CAG repeat number <21 (0.841±0.129 g/cm²) (P=0.007). The association remained significant after adjustment for age, years since menopause (YSM) and BMI (P=0.016). Additionally, calcium concentration in serum was associated with the (CAG)n polymorphism. Calcium concentration in serum was higher in women with biallelic mean CAG repeat number ≥21 (9.88±0.48 mg/dl) than in women with biallelic mean CAG repeat number <21 (9.73±0.44 mg/dl) (P=0.017). No effect was observed on circulating levels of OPG and sRANKL.

Conclusions
The (CAG)n polymorphism of the AR gene may influence BMD at the lumbar spine in menopausal Greek women.

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Abstract withdrawn.

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Role of vitamin D levels and vitamin D supplementation on bone mineral density in Klinefelter syndrome

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Introduction
Decreased bone mineral density (BMD) in Klinefelter syndrome (KS) is frequent and it has been traditionally related to low testosterone levels. However, low BMD can be observed also in patients with normal testosterone levels and testosterone replacement therapy does not necessarily increase bone mass in these patients. Nothing is known about vitamin D levels and supplementation in KS. In this study we determine vitamin D status and bone mass in KS subjects and compare the efficacy of testosterone therapy and vitamin D supplementation on BMD.

Methods
A total of 127 non-mosaic KS patients and 60 age-matched male controls were evaluated with reproductive hormones, 25-hydroxyvitamin D, PTH, and bone densitometry by DEXA. Patients with hypogonadism and/or 25-hydroxyvitamin D deficiency were treated with testosterone-gel 2% and/or calcifediol and re-evaluated after 24 months of treatment.

Results
25-hydroxyvitamin D levels were significantly lower in KS patients with respect to controls, and they had significantly lower lumbar and femoral BMD. The percentage of osteoporosis/osteopenia in subjects with 25-hydroxyvitamin D deficiency was higher with respect to subjects with normal 25-hydroxyvitamin D and was not related to the presence/absence of low testosterone levels. Subjects treated with calcifediol or testosterone + calcifediol had a significant increase in lumbar BMD after treatment. No difference was found in testosterone-treated group.

Conclusions
These data highlight that low 25-hydroxyvitamin D levels have a more critical role than low testosterone levels in inducing low BMD in KS subjects. Furthermore, vitamin D supplementation seems to be more effective than testosterone replacement therapy alone in increasing BMD.

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Phenotype–genotype correlation in a series of 131 patients studied for calcium-sensing receptor gene

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Calcium-sensing receptor gene (CASR) loss-of-function mutations lead to familial hypocalciuric hypercalcaemia (FHH), neonatal severe hyperparathyroidism, and primary hyperparathyroidism. FFH is characterized by mild hypercalcaemia, hypocalciuria, calcium clearance/creatinine clearance (Ca/Cr) <0.01, normal or high PTH level. Nevertheless the phenotype may vary (Thakker 2012). The aim of this work was to compare the phenotypes of patients bearing or not a pathogenic CASR-mutation. Patients included (n = 131; 96 females, median (IQR) age 63 (40–77)) referred either for a calcium disorder not explained by sporadic hyperparathyroidism (n = 118) or pulmonary hypertension (n = 13 controls), were sequenced for CASR gene after written informed consent. Patients taking diuretics, phosphonates, lithium, with kidney failure, CaSR-antibodies or gain-of-function CASR-mutations had been excluded. Gender, age, nephrolithiasis, bone DEXA; blood calcium, phosphate, creatinine, 25-hydroxyvitamin D and PTH levels, 24-H calciuria, and Ca/Cr were compared according to the level of calciuria < 100, 100–105, or > 105 mg/l and the presence of a pathogenic CASR mutation. The CASR-mutated group (n = 21) showed higher calciuria (108 (110–119) mg/l vs 105 (99–110) mg/l) and lower PTH (50 (32–92) pg/ml vs 83 (52–107) pg/ml) than the non-mutated group (n = 110), with no difference for other parameters, especially 25-hydroxyvitamin D (27 (21–35) ng/ml vs 23 (15–33) ng/ml, calciumurea (120 (45–185) mg/l vs 123 (65–185) mg/l), and Ca/Cr (0.01 (0.00–0.02) vs 0.01 (0.01–0.02)). The non-mutated group included 51 normal CASR, 50 heterozygous, and nine homozygous or composite heterozygous variants. The comparison of these three sub-groups with the CASR-mutated group also differed for calciuria and PTH (P = 0.01). CASR-mutations and CASR-variants were identified respectively in none and 15 (5%) of the 28 patients with calciuria <100 mg/l, 4 (14%) and 14 (50%) of the 28 patients with calciuria between 100 and 105 mg/l, and 17 (22%) and 30 (40%) of the 75 patients with calciuria > 105 mg/l. Seven/13 (53%) patients tested without any calcium disorder bore CASR-variants.

Conclusion
50% of patients with calciuria < 105 mg/l showed a CASR-variant, whereas 40% with calciuria > 105 mg/l showed a CASR-mutation, with lower PTH levels, but no difference in terms of calciuria or (Ca/Cr) despite similar vitamin D status. Calciuria/PTH ratio could be a better marker of pathogenic CASR-mutation than (Ca/Cr) <0.01.

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Serum cystatin C levels were correlated with cardiometabolic features and cardiovascular diseases in patients with primary hyperparathyroidism

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Patients with primary hyperparathyroidism (PHPT) are at risk of chronic kidney disease (CKD). PHPT patients (n = 190, 146 females and 44 males, aged 59.7 ± 14.2 years) and non-hypertensive, non-diabetic age- and sex-matched healthy controls were evaluated for serum cystatin C and creatinine. PHPT patients and controls with established CKD were excluded. Serum cystatin C was measured by immunonephelometric assay and calculation of estimated glomerular filtration rate (eGFR) was based on serum creatinine and cystatin C (eGFRcr-cys) using the CKD-EPI equation. Serum cystatin C well correlated with serum creatinine in

PHPT patients (r = 0.594, P = 0.0001), while mean cystatin C level was significantly higher in PHPT patients than in healthy controls (0.93 ± 0.02 mg/l vs 0.78 ± 0.01 mg/l, P = 0.001). In particular, among PHPT patients with eGFRcr > 60 ml/min per 1.73 m², 18.4% had cystatin C levels > 1.03 mg/l (95th percentile of controls’ values), consistent with a ‘preclinical kidney disease’. These patients had higher HOMA-IR values and were more hypertensive. In PHPT patients, cystatin C levels positively correlated with total and ionized calcium (r = 0.151, P = 0.024 and r = 0.259, P = 0.004) and with PTH (r = -0.176, P = 0.01). Using the eGFRcr-cys equation, CKD (stages G3a, 3b, and 4) was diagnosed in 13.7% of PHPT patients. CKD–PHPT patients had higher total and ionized calcium, were older, more frequently males, heavier, more insulin-resistant and more frequently affected with hypertension. Any significant correlation with the occurrence of kidney stones could be detected. Regression analysis identified hypertension and HOMA-IR values as the independent variables able to predict eGFRcr-cys in PHPT patients. Considering the occurrence of cardiovascular diseases (CVD) (coronaropathy, arithmopathy, and cerebral vasculopathy), after adjustment for age and sex, CVD was positively correlated with cystatin C levels (β = 3.05 ± 0.109; P = 0.006) and negatively with eGFRcr-cys values (β = −0.005 ± 0.002; P = 0.011). In conclusion, elevated cystatin C levels were cross-sectionally associated with key CVD risk factors and with CVD diseases in PHPT patients as in the general population.

Disclosure
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**GP.11.01**

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**GP.11.02**

**Hypocalcaemia development in patients operated for primary hyperparathyroidism: can it be predicted preoperatively?**

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Introduction

Primary hyperparathyroidism (PHP) is a highly prevalent disease, which is treated most effectively by surgery. Postoperative hypocalcaemia, a morbidity of surgical treatment of parathyroidism, can prolong the hospital stay. The aim of this study was to identify the predictors of hypocalcaemia and hungry bone syndrome (HBS) in patients who undergo parathyroidectomy due to PHP.

Materials and methods

Preoperatively and on days 1 and 4, and month 6 postoperatively, the patients’ laboratory data including parathyroid hormone (PTH), calcium, phosphorus, 25-hydroxyvitamin D3 (25-OHD), albumin, magnesium, alkaline phosphatase (ALP), blood urea nitrogen (BUN), and TSH, free T3 and free T4 levels; and neck ultrasonography (US) and bone densitometry findings were recorded.

Results

Hypocalcaemia was observed in 63 (38.4%) of 164 patients on day 1 following parathyroidectomy. On the postoperative 6th month, permanent hypocalcaemia was present in 10 (6.1%) patients. HBS was observed in 22 (13.4%) of the patients who underwent parathyroidectomy due to PHP. Among the PHP-related parathyroidectomy patients, postoperative hypocalcaemia was observed more frequently among patients with parathyroid hyperplasia and those with osteoporosis. On the other hand, PTH, ALP, and BUN values were higher among patients who developed HBS. Additionally, HBS was observed more frequently among osteoporosis and parathyroid hyperplasia patients and those who had thyroidectomy simultaneously with parathyroidectomy.

Conclusion

As a result, a more thorough preoperative follow-up is recommended for patients with risk factors for hypocalcaemia and HBS development.

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**GP.11.03**

**The evaluation of central corneal and retinal thickness and intraocular pressure in patients with primary hyperparathyroidism**

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Introduction

Ocular changes are common in various endocrine disorders. However, there are only few studies reporting ocular changes in patients with primary hyperparathyroidism (PHPT). Here, we examined central corneal thickness (CCT) and retinal thickness (RT), intraocular pressure (IOP) and their relationships with serum intact parathyroid hormone (iPTH), calcium (Ca), and phosphorus levels in PHPT patients.

**Methods**

Thirty-seven patients with PHPT were included and compared with age- and sex-matched 43 controls. CCT, RT, and IOP were measured.

**Results**

There was no statistically significant difference in mean right and left RT between two groups (P=0.730 and P=0.530 respectively). Right CCT and IOP were significantly higher than controls (P=0.024 and P=0.038 respectively). However, no significant difference was found between groups concerning left CCT and IOP (P=0.415 and P=0.070 respectively). A negative correlation was observed between right CCT, and serum phosphorus and 24-h urine phosphorus levels (r=-0.391, P=0.017 and r=-0.393, P=0.021 respectively). Additionally, right IOP was negatively correlated with 24-h urine calcium levels (r=-0.331, P=0.049). Left CCT was negatively correlated with 24-h urine phosphorus levels (r=-0.348, P=0.044). Furthermore, negative correlation was found between left IOP and 24-h urine calcium levels (r=-0.396, P=0.017). No significant correlation was found between iPTH levels and right CCT, right RT, right IOP, left CCT, left RT, and left IOP levels (P>0.05 for all parameters). Also, serum Ca levels were not significantly correlated with right CCT, right RT, right IOP, left CCT, left RT, and left IOP levels (P>0.05 for all parameters).

**Conclusion**

In the literature, data about ocular diseases and PHPT are rare. In this study, we observed right CCT and IOP values of patients with PHPT were significantly higher than controls. We consider that the identification of ocular aspects of PHPT is significant, and further studies related to the condition are required.

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**GP.11.04**

**Secondary hyperparathyroidism in HIV patients and its relation to cardiovascular risk factor**

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Rationale

Low level of vitamin D can results in secondary hyperparathyroidism (SH) that has been linked to increased cardiovascular risk in general population. However, the spectrum of cardiovascular risk associated with SH in HIV-infected adults remains uncertain. Our main aim was to determine its potential association with different markers of cardiovascular risk in HIV-infected adults.

**Methods**

Cross-sectional study. Clinical data related to obesity, blood pressure, glucose metabolism, lipid profile, toxics use, and renal function were recorded. Hypovitaminosis D was defined by 25-hydroxy vitamin D level <30 ng/ml. SH was defined by parathyroid hormone >65 pg/ml in presence of hypovitaminosis D. Patients were divided into three groups according to status of vitamin D and the presence of SH: A) SH and hypovitaminosis D, B) hypovitaminosis D without SH, and C) vitamin D sufficient.

**Results**

104 HIV patients were included. Median vitamin D was 30.6±13.6 ng/ml. Prevalence of hypovitaminosis D and SH were 53.8 and 13.5% respectively. Quantitatively, all parameters related to cardiovascular risk, except fasting glycaemia, were higher among patients of group A, but only levels of total cholesterol, LDL, and triglycerides reached significant difference (P=0.002; 0.004; and 0.03 respectively). Also, prevalence of obesity (BMI ≥30 kg/m²) was higher in patients that developed SH (group A) when compared to groups B and C (28.6% vs 19% vs 2%, respectively; P=0.004). In multivariate analysis, SH was not associated with any cardiovascular risk factor.

**Conclusions**

Though, HIV-infected patients with SH due to hypovitaminosis D have worse cardiovascular risk profile, we can not conclude that SH is independently associated with major risk factors. Nevertheless, we think these patients require a more thorough preoperative follow-up is recommended for patients with risk factors for hypocalcaemia and HBS development.

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**GP.11.05**

**Determination of reference values for serum total 1,25-dihydroxyvitamin D3 using an extensively validated 2D ID-UPLC–MS/MS method**

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The 2D ID-UPLC–MS/MS method (Xevo TQ-S tandem quadrupole mass spectrometer and an Acquity UPLC system (Waters)), able to measure picomolar concentrations of 1,25-dihydroxyvitamin D3 in human serum, was extensively validated with regard to sensitivity, specificity, and robustness. Intra-assay variation was <5% and inter-assay variation was <7.5% over the whole dynamic range. Limit of quantitation was 3.4 pmol/l. Our method correlated well with a published 1,25-dihydroxyvitamin D3 LC–MS/MS method. The female part of the reference group showed a statistically significant higher average 1,25-dihydroxyvitamin D3 levels in premenopausal women taking oral contraceptive pills compared to postmenopausal women suggesting that this effect is estrogen-related.

In conclusion, we described a 2D ID-UPLC–MS/MS method able to measure 1,25-dihydroxyvitamin D3 with a high sensitivity and precision. In addition, reference values for 1,25-dihydroxyvitamin D3 were determined using this method.

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**GP.11.06**

**Relationship between serum 25-hydroxvitamin D3 and adipose tissue vitamin D receptor gene expression with obesity and type 2 diabetes**

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**Introduction**

25-hydroxvitamin D3 (25(OH)D3) deficiency has been associated with diabetes and obesity. However, the mechanisms underlying these relationships are not completely understood. Vitamin D receptor (VDR) is expressed in adipose tissue; it has been reported a higher expression in obese patients than in lean subjects, suggesting a differential vitamin D dynamics in adipose tissue according to the obesity degree. In addition, 1,25-dihydroxyvitamin D3 (1,25(OH)2D3) is able to modify VDR gene expression in mice 3T3-L1 adipocytes.

**Objective**

To analyse plasma 25(OH)D3 and VDR gene expression in adipose tissue according to BMI and glycemic status. To evaluate the influence of 1,25(OH)2D3 and VDR gene expression in human adipose tissue cultures.

**Materials and methods**

We recruited and classified 119 subjects according to their BMI (lean, overweight, obese, and morbidly obese subjects) and to their glycemic status: normoglycemic (NG) and prediabetic/diabetic (P/D) patients. We measure plasma 25(OH)D3 and parathyroid hormone (PTH) levels as well as VDR gene expression in visceral adipose tissue. Adipose tissue from morbidly obese (ATMO) and lean (ATL) donors were cultured and treated with a range of 1,25(OH)2D3 concentrations.

**Results**

Plasma 25(OH)D3 were lower in P/D patients compared to NG subjects in the four BMI groups (P < 0.05). Plasma 25(OH)D3 levels correlated negatively with HOMA-IR (P < 0.01) and glucose (P < 0.05). No differences were found in plasma 25(OH)D3 levels according to the BMI. There was a higher VDR gene expression levels in morbidly obese patients (P < 0.05) compared to groups with lower BMI. 1,25(OH)2D3 increased VDR gene expression in ATMO, but not in ATL (P < 0.05).

**Conclusion**

Plasma 25(OH)D3 are diminished in P/D patients compared to NG subjects independent of BMI and are closely related with glucose metabolism variables, suggesting that vitamin D deficiency is associated more with carbohydrate metabolism than with obesity. Adipose tissue VDR gene expression was significantly higher in morbidly obese patients than in the other BMI groups and its regulation by 1,25(OH)2D3 was only demonstrated in morbidly obese subjects.

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**GP.11.07**

**Tainted vitamin D responses under methyl donor deficiency of the pre-osteoblast cells are caused by a decreased VDR expression and a disruption of PGC-1α: VDR co-regulators complex**

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Folate and cobalamins are methyl donors (MD) needed for synthesis of methionine, precursor of 3-adenosylmethionine (SAM), the substrate of methylation in epigenetic, and epigenomic pathways. The MD deficiency (MDD) leads to a decrease in SAM/SAH ratio and hyperhomocysteinemia, which has been related to osteoprotic in humans and disruption of development of epiphyseal cartilage in rat. However, the underlying molecular mechanisms remain elusive.

**Method**

We studied the consequences of MDD on proliferation and differentiation of MG-63 pre-osteoblasts.

**Results**

1,25(OH)2D3 and vehicle treated MDD cells displayed a significantly decreased nuclear expression of PGC-1α/VDR complex compared to controls. The impaired activation of PGC-1α in deficiency resulted from its decreased methylation related to the blunted methyl-transferase activity, and increased cellular concentration of SAH, a potent inhibitor of PRMT1. Hypomethylation of PGC-1α dramatically affected expression of differentiation markers in deficient cells with a strong increase in PPARY and its targets (adiponectin and ERRα), and a significantly decreased expression and activity of bALP. The MDD induced a marked increase in expression of the HSP90. Although primarily cytoplasmic, HSP90 has been shown to translocate to nucleus and play a role in regulation of NR activity. In this study, strong HSP90-VDR interactions in the MDD cells make VDR less likely to bind to the PGC-1α. We suppose that the HSP90-VDR impaired formation of the VDR/NR heterodimer, with an increased expression of PPARY targets (adiponectin and ERRα) leading to an adipogenic phenotype.

**Conclusion**

In conclusion, this is the first evidence demonstrating existence of functional interactions between PGC-1α and VDR, its key role for normal functioning of the VDR-NR transcriptional co-regulation during osteoblast differentiation, and a dramatic effect of MDD on this co-regulatory network.

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**GP.11.08**

**Associations of visceral and hepatic fat with serum 25-hydroxyvitamin D concentrations**

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**Introduction**

Obesity is associated with lower serum 25-hydroxyvitamin D (25(OH)D) concentrations. A major explanatory hypothesis is that vitamin D is sequestered...
by adipose tissue. Another hypothesis is a decreased hepatic activation by 25-hydroxylation in obese individuals. Because adipose tissue has different characteristics and functions in different parts of the body an important question is whether serum 25(OH)D is more strongly related to visceral VAT, hepatic, or total body fat (TBF).

**Methods**

In the Netherlands Epidemiology of Obesity (NEO) study, a cohort of 6671 men and women, VAT was assessed by MRI in combination with 1H MR spectroscopy of hepatic triglyceride content (HTGC) in 2076 participants. TBF was determined with bioelectrical impedance analysis and serum 25(OH)D was measured. We performed linear regression of VAT and HTGC on serum 25(OH)D, adjusted for age, sex, ethnicity, smoking, education, alcohol consumption, and TBF.

**Results**

After exclusion of alcohol abuse (n = 117) and missing data (n = 24), 1935 participants were analysed (mean and ± S.D. of age: 55 (6) years, BMI: 26 (4) kg/m², VAT: 87 (54) cm², HTGC: 5.6 (7.7) cm³, serum 25(OH)D: 62.7 (26.7) nmol/l, 56% women). Per S.D. of VAT serum 25(OH)D was 5.3 nmol/l (95% CI −7.5, −3.2 lower, and per S.D. HTGC 3.3 nmol/l (−3.6, −0.4) lower. Per S.D. of total body fat serum 25(OH)D was 5.7 nmol/l (−8.1, −3.2) lower. In a joint model including VAT, HTGC, and TBF, only VAT remained negatively associated with serum 25(OH)D (−4.9 nmol/l, 7.1, −2.7 per S.D.).

**Conclusion**

The major finding of the present study is that although all markers of total and regional adiposity were associated with lower serum 25(OH)D, joint models showed that visceral adipose tissue was more strongly related to lower serum 25(OH)D concentrations.

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**Diabetes and obesity - Translational diabetes**

**GP.12.01**

Comparison of umbilical cord ghrelin concentrations in full-term pregnant women with or without gestational diabetes

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**Purpose**

The purpose of this study was to analyse ghrelin concentrations in the umbilical cord of pregnant women with a diagnosis of gestational diabetes mellitus. The relationship between ghrelin concentrations and birth weights was investigated.

**Methods**

Sixty pregnant women with gestational diabetes mellitus and 64 healthy pregnant women with three oral glucose tolerance test results within normal limits were included in the study. Following birth but before extraction of the placenta, 10 ml blood samples were drawn from the umbilical vein in both groups. Ghrelin concentrations were measured.

**Results**

The mean birth weights of the babies born to mothers with GDM were higher than those in the control group (P = 0.04). The cord blood ghrelin levels in pregnant women with GDM were significantly lower than those of the healthy women in the control group (879.6 ± 972.2 pg/ml; P = 0.03). The umbilical cord blood ghrelin concentrations in pregnant women with GDM undergoing insulin therapy were significantly lower than those of the control group (792.61 ± 792.2 pg/ml; P = 0.01). Inverse correlations were detected between umbilical cord blood ghrelin levels and birth weights of the babies both in the group with GDM patients (r = −0.785; P = 0.001) and in the control group (r = −0.749; P = 0.001).

**Conclusions**

In pregnant women with GDM, umbilical cord ghrelin concentrations are closely related to the birth weights of the babies. Ghrelin presumably may be among the factors influencing foetal development potentially with its GH stimulating effects or by means of other mechanisms.

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**GP.11.09**

Physical performance in women with vitamin D deficiency

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**Introduction**

VD deficiency is associated with the atrophy of muscle fibres (predominantly type II). This leads to decreased muscle force and general physical performance.

**Objective**

To analyse the relationship between the serum concentration of 25-hydroxy vitamin D (25OHD), balance and physical performance in women with VD deficiency and the effect of VD supplementation or treatment with a VD analog. Materials and methods

We analysed 105 women of various ages with VD deficiency defined as a serum 25OHD concentration of ≤ 50 nmol/l. The subjects were aged between 20 and 83 years old (mean ± S.D.: 51.95 ± 12.77 years). The mean baseline 25OHD concentration was 12.68 ± 5.77 nmol/ml (mean ± S.D.). The Tinetti balance subscore was significantly correlated with the concentration of 25OHD (P = 0.022). The mean results at the TUG and CRT tests were 8.91 ± 2.46 and 15.34 ± 5.58 s respectively. After treatment, the mean results at TUG and CRT test became 8.5 ± 2.17 and 14.56 ± 5.56 s respectively (P = 0.000 compared to baseline) representing a mean change of −4.9 and −7.33% respectively. The global Tinetti score and the subscores for balance and posture also improved significantly compared to baseline (P = 0.000 for total score and balance subscore and P = 0.033 for posture). The results were significantly better in the subgroup treated with alfacalcidol compared to the subgroup offered cholecalciferol for TUG (P = 0.012) but not for CRT (P = 0.074).

**Conclusion**

The major finding of the present study is that VD deficiency is significantly correlated with poor physical performance and impairment of balance and the effects are partially reversible with either VD supplementation or active VD analogs (alfacalcidol).

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**GP.12.02**

EATM regulates the NADPH-oxidases of erythrocyte membranes and serum of patients with types 1 and 2 diabetes ex vivo

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**Introduction**

Embryonal antinouveau modulator of Mitochondry (EATM) reveals a hypoglycemnic effect in streptozotocin-induced diabetes in rats. The aim of the work was to determine the influence of EATM on the process of releasing of Nox of erythrocyte membranes (EM) and serum of patients with diabetes type 1 and 2. Materials and methods

The study included 12 patients with type 1 diabetes, 12 patients with type 2 diabetes and 12 healthy volunteers. Isolation of Nox fractions of purified EM and blood serum was performed by ion-exchange chromatography. The Nox amount was determined at 530 nm. Gs-producing activity of Nox isoforms was determined by nitroetetrazolium blue. The statistical analysis was performed by one-way ANOVA. The study was approved by the Local Ethics Committee of the YSMU.

**Results**

It was shown, that the Nox release in EM of type 2 and 1 diabetes is higher by 83.3 ± 7.4% and 58.4 ± 6.5%, respectively, compared with donor blood. The addition of EATM resulted in suppression of the process of the Nox release in EM in diabetes type 2 and 1 and healthy donors by 45.5 ± 6.2%, 31.6 ± 4.4% and 25.1 ± 3.7%, respectively. In the same conditions the increase of releasing of the extracellular Nox from the blood serum in diabetes type 2 and 1 is up by 109.2 ± 8.7% and 45.4 ± 5.5% respectively. Addition of EATM reduced activity of eNox by 47.9 ± 4.4%, 31.3 ± 2.9% and 29.3 ± 3.2%, respectively.

**Conclusion**

The suppression of the releasing Nox and eNox of EM and serum exosomes in diabetes type 1 and 2 may be apparently a novel mechanism of membrane
stabilising effect of the EATM et vivo. This gives some scientific term for EATM as an agent, which helps to stabilise the EM and exosomes in diabetes type 1 and especially type 2 et vivo.

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GP.12.03
Can physical activity modify the impact of the genes on the incidence of type 2 diabetes mellitus? 
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The exact mechanism of the development of T2DM is still unclear, however, it is known that an important role is played by both environmental and genetic factors. In this study we focused on describing the interactions between environmental and genetic factors and answering the question whether physical activity can modify the impact of the genes on the incidence of T2DM. We recruited 921 subjects (median age: 38 years; 49.7% male; mean BMI: 28.1) from the cohort 1000 Polish Longitudinal University Study (PLUS). PA has been assessed using International Physical Activity Questionnaire, and 37 single nucleotide polymorphisms (SNPs) associated with T2DM in GWAS have been genotyped, to explore interaction between the SNPs and the level of PA on the incidence of T2DM. Genetic risk score (GRS) as a weighted sum of risk alleles have been calculated. We also calculated the percentage of T2DM cases within each of the four strata given by high and low GRS and PA by using R software. To explore GRS and PA interactions, we examined associations of PA with T2DM in each group. The incidence of T2DM was lower among physically active individuals in high GRS group (6.6% in high PA class and 13.8% in low PA class, P < 0.03) as well as in low GRS group (4.4% in high PA class vs 8.7% in low PA class, P < 0.03). We also found that individuals with TT variant in rs10885122 (ADRA2A) has slightly lower values of average PA compared to those with TG and GG genotypes (P < 0.006). In our study we proved that the genetic predisposition to T2DM can be reduced by increasing the PA, even among patients at high genetic risk. This allows to conclude that, through the use of physical activity we can reduce the incidence of T2DM, even in patients with a genetic predisposition.

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GP.12.04
Efficacy of autologous bone marrow derived mesenchymal stem cell transplantation in T2DM: a randomised placebo-controlled study
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Introduction
There is a growing interest in cell-based therapies in T2DM as β-cell failure is progressive and inexorable. This study evaluates the efficacy of autologous bone marrow-derived mesenchymal stem cell transplantation (ABM-MSCT) in T2DM.

Methods
This prospective, randomised, single-blinded placebo-controlled study enrolled 20 patients with triple oral hypoglycaemic drug failure and requiring insulin ≥0.4 Units/kg per day for achieving euglycaemia (HbA1c ≤7.5%). They were randomly assigned to mesenchymal stem cells (MSCs) group (n=10) who received ABM-MSCT through targeted approach, while control arm (n=10) underwent sham procedure and were followed for 6 months. The efficacy of intervention was assessed by gold standard method ‘hypeglycaemic clamp’ to estimate C-peptide response. The primary endpoint was a reduction in insulin requirement by 50% from baseline, while maintaining HbA1c ≤7%.

Results
Six out of the 10 (60%) patients in the ABM-MSCT, while 1 (10%) in the control group achieved the primary endpoint (P=0.05). The insulin requirement decreased by 45% in the ABM-MSCT group from 45.5 (34.0–52.2) IU/day to 25 (15.0–32.5) IU/day (P=0.0001), while in controls it decreased by 4% from 52.0 (40.0–82.0) IU/day to 50 (22.0–58.0) IU/day (P=0.001) with significant reduction between both the groups at 6 months (P=0.047). There was a modest but significant decrease in HbA1c in cases from 6.9% (6.6–7.0%) to 6.8% (6.1–
7.2%) (P=0.001) as well as in controls from 6.6% (6.1–6.8%) to 6.2% (6.0–6.2%) (P=0.001), but it was not significant between the groups (P=0.32). There was a significant decrease in 2nd phase C peptide response during hyperglycaemic clamp (P=0.004) and HOMA-β (0.04) without any significant change in HOMA-IR (P=0.08).

Conclusion
The ABM-MSCT results in decrease in insulin requirement while maintaining HbA1c ≤7%. However, the mechanism/s related to improvement in glycaemia remains elusive.

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Increased levels of Dickkopf-1 may indicate lower osteoblast signaling, predisposing to lower bone mineral density in children and adolescents with type 1 diabetes mellitus

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Introduction

T1DM is a risk factor for reduced bone mass, disrupting several bone metabolic pathways. Dickkopf-1 is an inhibitor of the Wnt/b-catenin bone metabolic pathway. Increased fracture risk and elevated Dickkopf-1 levels have been documented in adult patients with T2DM. No relevant data exist on childhood T1DM. Our aim was to study plasma Dickkopf-1 concentration in children and adolescents with T1DM and controls and to correlate Dickkopf-1 levels with metabolic bone markers and bone mineral density (BMD).

Methods

Forty children and adolescents with T1DM were evaluated (mean ± s.d. age: 13.04 ± 3.53 years, T1DM duration: 5.15 ± 3.33 years), along with 40 healthy matched controls (mean ± s.d. age: 12.99 ± 3.33 years). Dickkopf-1, Sclerostin, osteocalcin, C-telopeptide crosslinks-CTX, electrolytes, PTH, total 25(OH) D were measured, while lumbar spine and total body BMD were evaluated.

Results

BMD was significantly lower in T1DM patients than controls. Dickkopf-1 levels demonstrated a Gaussian distribution, with higher levels in patients with T1DM (5.34 ± 4.04 pmol/l, P = 0.0194). A trend for lower values was found in girls (13.36 ± 4.04 pmol/l vs 11.72 ± 5.14 pmol/l, P = 0.06) and in pubertal children (13.61 ± 2.487 ± 11.83 ± 4.56 pmol/l, P = 0.054). Dickkopf-1 correlated with Sclerostin and L1-L4 BMD z-score only in controls and with Osteoprotegerin and i-Phosphorus only in patients, while in both groups a significant correlation with i-CTX and GLP-1 was logarithmized. A significant correlation of Dickkopf-1 with IGF-1 and insulin dose was also shown in patients.

Conclusion

T1DM children and adolescents had higher levels of Dickkopf-1 than controls, indicating a downregulated Wnt signalling system and possible lower osteoblast activation that could be associated with T1DM osteopathy.

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Diabetes and obesity – Translational cardiovascular and obesity

Investigating chemerin/CMKLR1 signalling as a novel link between obesity and inflammatory bowel disease

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Background

Chemerin is a recently identified adipocyte-secreted signalling molecule (adipokine) that regulates adipocyte differentiation, metabolism, and inflammation through activation of the cognate receptor Chemokine-Like Receptor 1 (CMKLR1). Circulating chemerin levels are increased in obese patients as well as in patients with inflammatory bowel disease (IBD) such as Crohn’s disease and ulcerative colitis. Increased white adipose tissue mass (WAT) and resultant changes in the secretion of several adipokines have been shown to negatively impact the severity and treatment of IBD. Therefore, we hypothesized that chemerin/CMKLR1 signalling represents a novel link between obesity and IBD.

Objectives

To determine whether modulation of chemerin/CMKLR1 signalling impacts weight loss, clinical illness, and colonic inflammation associated with the onset of dextran sodium sulfate (DSS)-induced colitis in mice.

Results

Chemerin and CMKLR1 expression increased in the cecum and distal colon, while CMKLR1 expression decreased in WAT of DSS-treated mice. Following DSS treatment, WT mice had significantly higher chemerin levels both in the colon and circulation. Moreover, injection of bioactive chemerin into WT mice resulted in greater weight loss and colonic inflammation compared to vehicle control. Consistent with this, CMKLR1 knockout mice exhibited decreased early weight loss and a slower onset of clinical illness compared to WT controls. However, CMKLR1-null mice exhibited similar levels of colonic inflammation and clinical illness compared to WT littermates at the final endpoint.

Conclusions

Increased levels of circulating chemerin exacerbated the severity of DSS-induced colitis and CMKLR1-null mice had a delayed onset of colitis. This suggests that chemerin/CMKLR1 signalling modulates the development of IBD.

Disclosure

This work was supported by the Canadian Institutes of Health Research (CIHR).

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Screening for genetic and structural variation in the NPY2R gene in obese children and adolescents


Department of Medical Genetics, University of Antwerp, Antwerp, Belgium; Department of Endocrinology, Diabetology and Metabolic Diseases, Antwerp University Hospital, Antwerp, Belgium; Department of Pediatrics, Jessa Hospital, Hasselt, Belgium; Department of Pediatrics, Antwerp University Hospital, Antwerp, Belgium.

Objective

NPY2R is a G-protein-coupled receptor which is highly expressed in orexigenic NPY/AGRP neurons within the arcuate nucleus, a major integrator of appetite changes in the secretion of several adipokines have been shown to negatively impact the severity and treatment of IBD. Therefore, we hypothesized that chemerin/CMKLR1 signalling represents a novel link between obesity and IBD.

Objectives

To determine whether modulation of chemerin/CMKLR1 signalling impacts weight loss, clinical illness, and colonic inflammation associated with the onset of dextran sodium sulfate (DSS)-induced colitis in mice.

Results

Chemerin and CMKLR1 expression increased in the cecum and distal colon, while CMKLR1 expression decreased in WAT of DSS-treated mice. Following DSS treatment, WT mice had significantly higher chemerin levels both in the colon and circulation. Moreover, injection of bioactive chemerin into WT mice resulted in greater weight loss and colonic inflammation compared to vehicle control. Consistent with this, CMKLR1 knockout mice exhibited decreased early weight loss and a slower onset of clinical illness compared to WT controls. However, CMKLR1-null mice exhibited similar levels of colonic inflammation and clinical illness compared to WT littermates at the final endpoint.

Conclusions

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Objective

NPY2R is a G-protein-coupled receptor which is highly expressed in orexigenic NPY/AGRP neurons within the arcuate nucleus, a major integrator of appetite

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control in the hypothalamus. Genetic evidence coming from animal and association studies, has identified NPY2R as a candidate gene for obesity. Therefore we have designed an extensive mutation and CNV-analysis investigating the prevalence of genetic and structural variation in NPY2R.

Design and methods
In the first part of this study we screened 306 obese children and adolescents and 300 healthy lean individuals for mutations in the NPY2R coding region with high-resolution melting curve analysis. Direct sequencing was performed for samples with melting patterns deviating from WT. In the second part of this study, Multiplex Amplicon Quantification (MAQ) analysis was performed in 306 obese children and adolescents to detect copy number variation (CNV) in NPY2R.

Results
Mutation analysis resulted in the identification of one rare non-synonymous heterozygous variant F87I in an obese patient. Furthermore, we identified five different synonymous variants of which three (L53L, G326G and G370G) could solely be detected among obese children and two (P105P and A278A) were only present in lean individuals. L53L was identified among three different obese patients and was not present in the control population. MAQ analysis could not identify copy number variation in the NPY2R region in our population.

Conclusion
By performing in silico analysis, we determined that the F87I variant is probably damaging to the protein structure and might have a disease causing effect. Further functional testing will be necessary to fully understand the impact on NPY2R.

As we could not identify any CNV in the NPY2R region, structural variation in NPY2R is not likely to cause obesity.

Disclosure
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GP.13.03
Effects of dietary glycemic properties on markers of inflammation, insulin resistance and body composition in postmenopausal women
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Whether high glycemic index/glycaemic load (GI/GL) diets increase low-grade inflammation leading to changes in body composition and risk for chronic illness remains uncertain. We recently completed a randomised, double-blind study comparing the effects of a 45 g whey protein supplement (PRO) and an isocaloric maltodextrin supplement (CHO) on bone density and body composition in older adults. The study afforded an opportunity to elucidate the metabolic and reproductive/gonadotropic impact of various obesogenic insults in the female rat, with special attention to the influence of the loss of ovarian secretion, as model of menopause. To this end, we implemented a series of neuroendocrine studies on the metabolic and gonadotropic consequences of sequential obesogenic insults, namely, postnatal over-nutrition (SL) and high fat diet (HFD) after weaning, in gonadal-intact and ovariec-tomized (OVX) female rats. In young (4-mo) cyclic females, SL or HFD caused similar increases in body weight; yet, only HFD evoked additional metabolic perturbations, some of which were worsened by precedent SL. In addition, HFD caused a concomitant decrease in LH and estradiol levels, and suppressed Kiss1 expression in the arcuate nucleus (ARC) of the hypothalamus in 4-mo females, while persistent HFD up to 10-mo induced also suppression of LH responses to kisspeptin-10. OVX caused a severe and rapid deterioration of the metabolic profile, with overweight, increased energy intake and deregulation of leptin and glucose/insulin levels; effects whose magnitude was similar, if not higher than HFD. Summation of previous obesogenic insults maximally increased body weight, basal leptin, insulin and glucose levels, and glucose intolerance. Yet, OVX obliterated the inhibitory effects of overweight/HFD on gonadotropin levels and ARC Kiss1 expression, which were heightened due to the loss of negative feedback. In sum, our study characterizes the metabolic and gonadotropic effects of sequential exposures to obesogenic insults, and their interactions with ovarian secretions. Our data document the deleterious consequences of overweight on the female gonadotropic axis, via impairment of Kiss1 system, and substantiate the dramatic impact of OVX, as menopausal model, on the metabolic profile, especially when combined with preceding obesogenic insults.

Disclosure
This work was supported by grant BFU2011-025021 (Ministerio de Economı´a and Competitividad, Spain; co-funded with EU funds from FEDER Program); Projects P08-CVI-03788 and P12-FQM-01943 (Junta de Andalucı´a, Spain); EU research contract DEER FP7-E.

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GP.13.05
The effects of cross-sex hormone therapy on body weight and fat percentage in transgender individuals
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Introduction
Cross-sex hormone therapy is part of the treatment of individuals with gender dysphoria and affects several factors such as body composition and thereby cardiovascular risk. However, little is known about the specific effects on body weight and fat percentage in the first year of treatment.

Aim
The aim of this study is to examine the effects of cross-sex hormones on body weight and total fat percentage during the first year of treatment.

Methods
This prospective study (part of the ENIGI project) included 140 patients that completed one year of treatment. 70 male-to-female individuals (MfIs) received
cyproterone acetate (50 mg/day). Of them, 31 MIFs were treated with an estradiol patch (200 µg/week) and 39 MIFs received estradiol valerate (2–4 mg/day). 70 female-to-male individuals (FMs) were treated, of which 39 FMs got testosterone esters intramuscular (250 mg/2 weeks) and 4 FMs received testosterone undecanoate intramuscular (1000 mg/12 weeks). 27 FMs were treated with testosterone gel (50 mg/day). At the start and after 12 months of treatment their body weight was measured and a DEXA was obtained.

Results
At baseline the mean body weight of the MIFs was 77.5 kg (s.d. ± 16.8), which in one year increased to 79.7 kg (s.d. ± 17.0) with a mean difference of 2.2 kg (95% CI 0.7–3.8). Their mean total fat percentage increased with 4.0% (95% CI 3.0–5.0), from 25.0 to 29.0%. The mean body weight of the MIFs increased from 69.1 kg (s.d. ± 15.0) to 72.2 kg (s.d. ± 14.7) with a mean difference of 3.1 kg (95% CI 2.0–4.3). In FMs, a 4.3% (95% CI −5.3 to −3.3) decrease in total fat percentage was seen, from 34.7 to 30.4%.

Conclusions
Despite an expected increase in fat percentage in MIFs and a decrease in FMs, total body weight increased in both groups. Further research is needed to elucidate the mechanism of weight gain during cross-sex hormone treatment.

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GP.13.06
Effects of testosterone replacement therapy on lean body mass, total fat mass, and insulin sensitivity in aging men with type 2 diabetes - a randomised, double-blinded, placebo-controlled trial
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Lowered testosterone levels may be observed in up to 50% of ageing men with type 2 diabetes (T2D). Testosterone replacement therapy (TRT) increases lean body mass in men with lowered testosterone levels and T2D, but the effect of TRT on glucose metabolism has not been evaluated by euglycemic hyperinsulinemic clamp.

We used gold standard methods to evaluate the effect of TRT on body composition, insulin sensitivity, and oxidative metabolism in men with T2D and lowered bio-available testosterone. Our main objective was to determine whether TRT could be a novel treatment for T2D in ageing men with lowered bio-available testosterone.

Research design and methods
A randomised, double-blinded, placebo-controlled study in 39 men, aged 50–70 years with bio-available testosterone levels <7.3 nmol/L and T2D treated with Metformin. Patients were randomized to testosterone gel (n=20) or placebo (n=19) for 24 weeks. Body composition was assessed by whole body Dual-energy X-ray Absorptiometry scans including our primary outcome, lean body mass. Whole-body insulin sensitivity was assessed by rate of insulin-stimulated glucose disposal during euglycemic hyperinsulinemic clamp. Substrate oxidation was evaluated by indirect calorimetry during euglycemic hyperinsulinemic clamp. Coefficients (b) represent the placebo-controlled mean effect of intervention.

Results
Lean body mass (b = 1.9 kg, P = 0.001) increased during TRT, while total fat mass (b = -1.3 kg, b = 0.009) and HDL cholesterol (b = -0.11 mmol/L, P = 0.009) decreased. Insulin-stimulated glucose disposal rate was unchanged during TRT compared to placebo (P = 0.28). Lipid and glucose oxidation during fasting and insulin stimulation were unchanged.

Conclusions
Insulin sensitivity was unchanged in men with T2D despite significant beneficial changes in lean body mass and total fat mass after 24 weeks TRT. Furthermore, HDL cholesterol levels were reduced during TRT. Our data do not suggest testosterone replacement therapy as a novel therapy for type 2 diabetes in ageing men.

Disclosure
This study was financially supported by the Nordic Novo Foundation, Odense University Hospital, Institute of Clinical Research at the University of Southern Denmark, the Region of Southern Denmark, Consultant Council Scholarship Committee of O.

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GP.13.07
Three out of four adult male patients with type 2 diabetes mellitus and symptomatic moderate to severe erectile dysfunction have hypogonadism
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Context
Studies suggest that 25–40% of men with type 2 diabetes mellitus (T2DM) have hypogonadism. Other studies have estimated that 40–50% of men with T2DM have erectile dysfunction (ED). Some guidelines suggest routine measurements of testosterone in all patients with T2DM.

Objectives
To estimate the prevalence of hypogonadism in adult male patients with type 2 diabetes mellitus and symptomatic erectile dysfunction.

Methods
Consecutive adult male patients (between 30 and 60 years) with ED and T2DM attending diabetic clinic in a tertiary hospital were recruited after informed consent. Patients with psychiatric illness, renal disease, liver disease, previous pelvic surgery and major neurological diseases were excluded. ED was graded using the International Index of Erectile Dysfunction (IIEF) questionnaire. Biochemical assessment of hypothalamic-pituitary-gonadal (HPG) axis was undertaken by collecting morning samples for serum luteinizing hormone, follicle stimulating hormone, prolactin and total testosterone. These were analyzed by electrochemiluminescence assays on an ELECSYS automated system. Patients were classified as either being eugonadal or having either hypogonadotropic hypogonadism (HH) or hypergonadotropic hypogonadism (HHG).

Results
Patients consented for the study with a mean age of 50.3 years and mean duration of diabetes of 5.9 years. Of them 102 patients completed all the study related procedures and were included in the analysis. 54 (52.9%) of men with T2DM and ED were eugonadal, 38 (37.3%) had HH and 10 (9.8%) had HHG. All 25 patients with mild ED (IIEF scores 17–21) were eugonadal. While of 28 patients with mild to moderate ED (IIEF scores 12–16), 24 (85.7%) were eugonadal and 4 (14.3%) had HH. Of the 16 patients with moderate ED (IIEF scores 8–11) 14 (25%) were eugonadal, 9 (56.3%) had HH and 3 (18.8%) had HHG. Among the 33 patients with severe ED (IIEF score 1–7) only 1 (3%) was eugonadal, 25 (75.8%) had HH and 7 (21.2%) had HHG (P = 0.0001).

Conclusions
Routine hormonal evaluations of the HPG axis is probably only required in patients with moderate to severe ED with type 2 diabetes. Over 75% of patients with moderate to severe ED have subnormal total testosterone levels.

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GP.13.08
Eating disorders are frequent among type 2 diabetic patients and are associated with worse metabolic and psychological outcomes: results from a cross sectional study in primary and secondary care settings
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Objectives
Diabetes and obesity – Translational cardiovascular and obesityData regarding the prevalence of eating disorders (ED) and their influence on clinical outcomes among patients with type 2 diabetes (T2DM) are scarce. Our aim is to investigate the frequency of positive screening for ED and, specifically binge eating disorder (BED), in a T2DM sample. To analyse whether there are any differences among T2DM subjects with a positive screening for ED or BED.

Research design and methods
320 subjects with T2DM were recruited randomly. All participants were evaluated for the presence of ED by completing the ‘Eating Attitudes Test-26’ (EAT26). In addition the ‘Questionnaire of Eating and Weight Patterns Revised’ (QEWP-R) for the screening of BED was also implemented. Sociodemographic, clinical and biochemical parameters were also recorded.

Results
According to EAT26, 14% of subjects screened positive for ED. Regarding QEWP-R, 16% had a positive screening for ED, with BED having a frequency of 12.2%, being the most prevalent one. There was a positive correlation between the scores obtained with the EAT26 and the Beck Depression Inventory (P = 0.0014). Patients with BED were younger (57.5 ± 11.1 vs 63.3 ± 10.3 years; P = 0.004), with a lesser T2DM duration (8.5 ± 6.1 vs 12.1 ± 9.6 years; P = 0.002).
Diabetes and obesity – Clinical diabetes

**GP.14.01**

What components drive the metabolic syndrome? Results from the population-based LifeLines Cohort Study

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**Introduction**

The metabolic syndrome (MetS) is a combination of unfavourable health factors including visceral obesity, dyslipidaemia, hypertension and impaired fasting glucose. It is also strongly associated with increased risk of cardiovascular disease (CVD) and type 2 diabetes. We assessed which factors contribute to the prevalence of MetS in people within different weight and age categories.

**Methods**

64,046 western European participants aged 18–80 years from the Dutch LifeLines Cohort study were categorised into three BMI classes (BMI <25, normal weight; BMI 25–30, overweight; BMI ≥30 kg/m², obese), and six age decades. MetS was defined according to the revised NCEP ATP III criteria. Within each BMI and age class, we determined the prevalence of all five MetS components.

**Results**

Prevalence of elevated blood pressure increased from 22% in the youngest age group (18–30 years) to 84% in the oldest age group (70–80 years). In these cohorts, the prevalence of excess waist circumference increased from 40% to 80%. The prevalence of increased serum triglycerides and fasting blood glucose was also the highest in the oldest age group (both 30%), while HDL-cholesterol remained strikingly constant with increasing age. In normal weight and overweight individuals, elevated blood pressure was the most common contributor to the presence of MetS. In obese individuals, elevated waist circumference, blood pressure and reduced HDL-cholesterol were the largest contributors.

**Conclusions**

The increase in prevalence of MetS with age in western European individuals is mainly driven by elevated blood pressure, and to a lesser extent by waist and HDL-cholesterol. As it is known that blood pressure increases with age, using a fixed 130/85 mmHg cut-off results in a disproportionate contribution of elevated blood pressure to the prevalence of MetS.

**Disclosure**

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**GP.14.02**

Changes of metabolic syndrome and its components in early adolescents through a 9.9 year community-based lifestyle intervention: Tehran Lipid and Glucose Study

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**Introduction**

While the unfavourable metabolic consequences of obesity have been clearly demonstrated at a population level, there is a wealth of evidence indicating the existence of individuals somehow protected from developing complications, named ‘metabolically healthy obese’. The aim of our study was to identify clinical and biological parameters independently associated with ‘metabolically healthy’ status.

**Patients and methods**

440 (303 women) extremely obese patients (mean BMI=45.33 ±8.82 kg/m²) were clinically (medical history, anthropometrics, blood pressure (BP)) and biologically (complete metabolic tests, adiponectin, CRP, TNF-α levels) in a research programme for bariatric surgery. Metabolically healthy obese status was alternatively defined using two criteria: i) absence of metabolic syndrome (ATPIII definition) and ii) insulin sensitivity (IS) — non-diabetic patients with HOMA <2.85 were considered IS+.

**Results**

Only 15.8% of patients (20.4% of women) fulfilled both criteria of metabolic health. Women were IS+ in a higher percentage than men (30.7% compared with 12.4%, P < 0.001). IS+ patients showed a lower general (BMI) and visceral (WC, WC/H) adiposity, lower CRP, lower levels of triglycerides and glucose metabolism. They also had lower BP, lower chronic inflammatory markers (TNF-α, CRP), but higher levels of adiponectin. Patients without metabolic syndrome were also younger, mostly women, had a higher insulin sensitivity, lower CRP level and increased concentration of adiponectin.

In logistic regression analysis, adiponectin (P = 0.011), VAI (P = 0.012) and uric acid (P = 0.031) remained significantly associated with insulin sensitivity. Area under ROC curve for the model was 0.815 (IC: 0.756–0.875; P < 0.001).

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In a similar model, independent determinant of metabolic syndrome were: adiponectin (P = 0.004), HOMA-IR (P = 0.011) and age (P < 0.001). Area under ROC curve for the model was 0.790 (0.744–0.853).

Conclusion
Adiponectin is an independent determinant of metabolically healthy obese status, disregarding the criteria used for its definition.

Disclosure
This work was partly supported by the Sectorial Operational Programme Human Resources Development (SOPHRD), financed by the European Social Fund and the Romanian Government under the contract number POSDRU 141531.

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GP.14.04
Parental obesity in association with offspring cognitive and psychomotor development at 4 years of age: the mother child ‘Rhea’ cohort in Crete, Greece
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Introduction
Animal studies suggest that maternal obesity may impact foetal brain structure and function and increase long-term susceptibility to neurodevelopmental and neuropsychiatric disorders. Few human studies have examined these associations with conflicting results. It is unclear if reported associations are due to genetic background or intrauterine mechanisms.

Objective
To investigate the association of maternal and paternal obesity status with offspring cognitive and psychomotor development at 4 years of age using data from a longitudinal, prospective pregnancy cohort, ‘Rhea’ study in Crete, Greece.

Design and methods
The present study includes 652 mother-child pairs, after excluding twin pregnancies and women with pre-gestational diabetes. Pre-pregnancy maternal BMI and paternal BMI were calculated at the first prenatal visit (mean: 12 weeks, s.d.: 1.5) neurodevelopment at 4 years was assessed by means of the McCarthy Scales of Children’s Abilities (MSCA). Emotional and behavioural development at 4 years was assessed by means of Strengths and Difficulties Questionnaire (SDQ) and Attention Deficit Hyperactivity Disorder (ADHD) Test. Multivariable linear regression models were used to estimate the effect of pre-pregnancy BMI and paternal BMI on child neurodevelopment at 4 years of age after adjusting for multiple confounders.

Results
Maternal obesity pre-pregnancy was associated with reduced general cognitive (score reduction: −2.51; 95% CI: −4.78, −0.24), quantitative (score reduction: −2.50 95% CI: −4.89, −0.11) and memory development scores (score reduction: −2.66 95% CI: −5.07, 0.26) at 4 years of age. These associations were more pronounced in girls compared to boys. No association was found between pre-pregnancy BMI and child emotional and behavioural development or ADHD symptoms at 4 years of age. Paternal BMI was not associated with offspring cognitive and behavioural development at 4 years of age.

Conclusion
Maternal pre-pregnancy BMI was associated with reduced cognitive development at preschool age. This association appeared more likely to be due to intrauterine mechanisms than shared family and social characteristics.

Disclosure
This work was supported by the ‘Program of prevention and early diagnosis of obesity and neurodevelopment disorders in preschool age children in the prefecture of Heraklion, Crete, Greece’ (NSRF 2007-2013 project, MIS 50580), co-f.

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GP.14.05
The effect of Roux-en-Y gastric bypass, sleeve gastrectomy and adjustable gastric banding on renal function and remission of metabolic disease: a five-year longitudinal study
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Introduction
There are few data on renal function following bariatric surgery. We evaluated the effect of Roux-en-Y gastric bypass (RYGB), adjustable gastric banding (AGB) and sleeve gastrectomy (SG) on renal function over a 5-year post-operative period. We also evaluate the effect of these procedures on remission of diabetes and hypertension.

Methods
Analysis of a prospectively collected database at Lille University Hospital. Patients were assessed pre-operatively and then at 1 and 5 years post-operatively.

Results
Subject undergoing RYGB (n = 190), AGB (n = 271) and SG (n = 16) were included. Estimated glomerular filtration rate (eGFR) increased following RYGB (95% CI: −2 to 101.4, P = 0.01) and AGB: 88.4 (−1 to 93.5, P = 0.02). In those with eGFR < 60 ml/min per 1.73 m² at baseline, eGFR improved over 5 years (52.4 (−2 to 68.47), 7 ml/min per 1.73 m², P = 0.01). RYGB induced remission of diabetes and pre-diabetes to a greater extent than AGB (43% vs 15%; P < 0.001). Remission of hypertension was also greater in the RYGB group at year 1 (32% vs 16%, P = 0.008) and year 5 (23% vs 11%, P = 0.02).

Conclusions
Bariatric surgery maintains eGFR over time. This may be due to the effect on blood pressure and glycaemia.

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GP.14.06
Higher HOMA levels and failed decrease in body fat can be considered unfavourable predictors of restoring euglycaemia in diabetic cirrhotic patients undergoing liver transplantation
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Introduction
Diabetes mellitus (DM) is a very common complication of cirrhosis (prevalence: 20–60%), primary due to increased hepatic insulin-resistance (IR). After liver transplantation (LT), DM recovers in 67% of cases, while 33% of patients remain diabetic because of a concomitant decreased beta cell function. The roles played by pre-transplant factors determining changes in glucose tolerance after LT are imperfectly known.

Aim of the study
To highlight any factors that predict increased risk of persistence of post-transplant glucose homeostasis alterations in diabetic cirrhotic patients undergoing LT.

Materials and methods
42 patients with liver cirrhosis, 31M/11F, age 53±9.9 years, underwent a metabolic and anthropometric evaluation, they underwent a bioelectrical impedance analysis (BIA) and an oral glucose tolerance test (OGTT) was performed to diagnose diabetes, before and 6 months after LT. Depending on OGTT results, patients were classified as Non Diabetic (ND) patients, who remain euglycaemic before and after LT, Diabetic (D) patients, who didn’t recover from diabetes after LT, or Regressors (R), who were diabetic and returned to euglycaemia after LT. No euglycaemic cirrhotic patients became diabetic after LT, so this group was not considered. IR was assessed with HOMA index, body fat was quantified with BIA (being BMI and waist circumference unreliable in cirrhotic patients because of the presence of ascites).

Results
Depending on this classification, our population was composed by 22 ND, 13 D and seven R patients. HOMA levels before LT were higher in D patients if compared to ND and R (7.7± 1.7 vs 3.1± 0.6 and 3.7 ± 1.8 respectively, P < 0.05).
Moreover, R showed a significant decrease in body fat, if compared to D patients ($\sim 13.3\%$ vs $1.5 \pm 0.2\%$, $P < 0.05$).

Conclusions
In diabetic cirrhotic patients undergoing LT, higher HOMA levels and failed decrease in body fat after LT can be considered unfavourable predictors of recovering from diabetes after transplantation.

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GP.14.07
Degree of control of type 2 diabetes in Spain according to individualised glycaemic targets
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Our objective was to estimate the distribution of Spanish diabetic patients attending to individualized glycaemic targets recommended by the ADA/EASD consensus with and without considering hypoglycaemia risk.

We conducted a cross-sectional study in a Spanish primary care setting between 2011 and 2012. A total of 5382 type 2 diabetic subjects under antihyperglycaemic treatment for at least 3 months prior to inclusion completed a study visit in which clinical data including age, diabetes duration, complications and treatment, and presence of a hypoglycaemia during the last year were collected. A capillary HbA1c was measured by the A1CNow + system. Patients were classified into different targets of HbA1c according to i) the ADA/EASD consensus without taking into account hypoglycaemia risk (presence of hypoglycaemia that required medical assistance during the past year and/or treatment with at least two insulin doses). ii) The ADA/EASD consensus taking into account hypoglycaemia risk. Mean HbA1c was 7.2 (1.2) % and 48.6% of our patients had an HbA1c <7%. According to the ADA/EASD strategy without taking into account hypoglycaemia risk, 15.9, 17.1 and 67% of the patients applied to glycaemic targets of <6.5, <7 and <8% and 68.5% were considered to have an adequate glycaemic control. On the other hand, according to the ADA/EASD strategy taking into account hypoglycaemia risk 14.9, 15.5 and 69.6% of the patients applied to glycaemic targets of <6.5, <7 and <8% and 67.4% of the patients were considered to have an adequate glycaemic control. The degree of concordance between both strategies in terms of classifying patients at a certain HbA1c target was 97.4% ($\kappa$ coefficient = 0.9413).

In conclusion, individualisation of glycaemic targets increases the proportion of patients considered adequately controlled. The inclusion of information regarding hypoglycaemia risk in the ADA/EASD strategy does not affect patient classification.

Disclosure
This work was funded by grants from Almirall.

DO: 10.1530/endoads.37.GP.14.07

GP.14.08
Factors associated with islet yield and insulin independence after total pancreatectomy and islet cell autotransplantation in patients with chronic pancreatitis utilising off-site islet isolation: Cleveland Clinic experience
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Context
Total pancreatectomy (TP) with islet cell autotransplantation (IAT) can reduce or prevent diabetes by preserving $\beta$-cell function, and is normally performed with on-site isolation laboratory facilities.

Objective
We examined factors associated with islet yield and metabolic outcomes in patients with chronic pancreatitis undergoing TP-IAT. We report our experience of TP-IAT with an off-site islet isolation laboratory.

Patients and methods
Data (August 2008–February 2014) were obtained from a TP-IAT database which included information from medical records, clinic visits, questionnaires and follow-up telephone calls. Each patient was assessed with pre- and post-operative 5-h mixed meal tolerance tests for metabolic measurements and with serial HbA1c determinations.

Results
Thirty-six patients with a mean age of 38 years (range 16–72 years) underwent TP-IAT for different aetiologies. At a median follow-up time of 28 months (range 3–66), 12 patients were insulin independent and 24 patients were on at least one insulin injection a day. Post-operatively, C-peptide levels ≥0.3 mg/ml were present in 23/33 (70%) of the patients, with a median fasting C-peptide value of 0.8 ng/ml (range <0.2–1.5 mg/ml). Those who were insulin independent were more likely to be female ($P=0.012$), have normal morphology on pre-operative pancreatic imaging ($P=0.011$), and have significantly higher median islet yield (6845 EU/kg, $n=12$ vs 3333 EU/kg, $n=24$, $P<0.001$).

Conclusions
Islet cell autotransplantation after total pancreatectomy performed in our facility with an off-site islet isolation laboratory shows islet yield and rates of insulin independence that are comparable to other large centres with on-site laboratories.

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Diabetes and obesity – basic

GP.15.01
Topical application of CD362+ human mesenchymal stem cells (cyndael-M) seeded in Excellagen scaffold augments wound healing and increases angiogenesis in a diabetic rabbit ulcer model
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Non-healing foot ulcers are a major complication in diabetic patients. Mesenchymal stem cells (MSCs) are known to promote angiogenesis with improved wound healing. Orbsen Therapeutics has identified a novel antibody (CD362+) which can be used to prospectively FACS-isolate CD362+CD45−MSCs from human bone marrow with enhanced MSC/MNC purity ratios of up to 1/4. Excellagen matrix was used to seed the cells as biomaterials are well reported to enhance viability and therapeutic efficacy of cells. In this study, 1 million of CD362+ MSCs and plastic adherent human MSCs were seeded in an Excellagen matrix and applied to cutaneous wounds in an alloxan-induced diabetic rabbit ear ulcer for a 1 week period. Statistical analysis between groups revealed that the wounds treated with an Excellagen-CD362+ cell treatment demonstrated increased percentage wound closure with more prominent neovascularisation. The wound sections were immunohistochemically stained by using CD31 and GSL-B4 lectin to study neovascularisation. In stereological analysis, significantly increased surface density, length density and reduced radial diffusion distance was observed in the Excellagen-CD362+ cell treated wound groups in comparison to untreated wounds. A subsequent study compared the beneficial effects of a combination treatment (IV delivery of cells at 2×106 cells/kg plus topical treatment) to topical treatment alone. A slight increase was observed in percentage wound healing in combination versus topical treated animals but this difference was not significant. There was no lowering of blood glucose levels in the combination treated animal groups over the seven day study period. Hence, with improved wound healing potential and augmenting angiogenesis, topical treatment with these specifically selected CD362+MSCs seeded in an Excellagen matrix may lead to a new therapeutic product to treat non-healing diabetic foot ulcers.

Disclosure
This research was supported by funding from EU FP7-HEALTH-2012-INNOVATION:1 grant number 305736 (REDDSTAR, Repair of Diabetic Damage by Stromal Cell Administration).

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Low plasma sex hormone-binding globulin (SHBG) levels are present in patients suffering chronic metabolic diseases, including non-alcoholic fatty liver disease (NAFLD). However, whether altered SHBG production plays a role in development and progression of this disease is unclear. To investigate SHBG involvement in NAFLD, we studied the effects of overexpressing SHBG in two mouse models, a genetically-induced model, by developing a double transgenic mouse by crossing the human SHBG transgenic mouse with the C57BL/6j-db/db mouse and a diet-induced model by feeding human SHBG transgenic mice and their WT littermates with high fructose diet (HFd) during 8 weeks. In addition, HepG2 cells were also used to explore the molecular mechanisms involved on the SHBG role in NAFLD. Moreover, human liver biopsies were used to corroborate the in vivo and in vitro findings. The SHBG overexpression in C57BL/6j-db/db mice significantly reduced liver weight and liver fat accumulation by reducing lipogenesis via acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS) and ATP citrate lyase (ACLY) downregulation. Next we showed that human SHBG transgenic mice were protected against NAFLD induced by HFd feeding that was evident in their WT littermate mice. The SHBG overexpression in this diet-induced NAFLD mouse model also reduced hepatic lipogenesis via ACC, FAS and ACLY downregulation. Furthermore, we showed a SHBG cell-autonomous effect on hepatocyte lipogenesis since SHBG overexpression reduced total triglyceride content by downregulating ACC mRNA and protein levels in HepG2 cells. Finally, the SHBG expression was inversely correlated with total triglycerides and ACC mRNA levels in human liver biopsies. Overall, we conclude that SHBG is a protective against NAFLD by inhibiting lipogenesis. Therefore, SHBG could be a new therapeutic target whereby increased expression may reduce NAFLD.

Disclosure
This work was supported by two Grants from the Instituto de Salud Carlos III (DMS) CP08/00058, PI09/144, PH12/01357 and CIBER de Diabetes y Enfermedades Metabólicas Asociadas an initiative of Instituto de Salud Carlos III (RF, AB, CH, AL, and DMS).

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Cardiomyopathy in the male obese diabetic db/db mice is alleviated by oxytocin treatment
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Oxytocin (OT) is involved in the regulation of energy metabolism and in the activation of cardio-protective mechanisms. We evaluated whether chronic treatment with OT could prevent the metabolic and cardiac abnormalities associated with diabetes and obesity using the db/db mouse model. Four-week-old male db/db mice and their lean non-diabetic littermates (db/+ ) serving as controls were treated with OT (125 ng/kg per h) or saline for a period of 12 weeks. Compared to db/+ mice, the saline-treated db/db mice developed obesity, hyperglycaemia and hyperinsulinaemia. These mice also exhibited a defective cardiac OT/natriuretic peptide system and developed systolic and diastolic dysfunction resulting from cardiomyocytes hypertrophy, fibrosis and apoptosis. These abnormalities were associated with increased ROS production, inflammation and suppressed AMP-kinase signalling pathway. The male db/db mice displayed reduced serum levels of adiponectin and adipin and elevated levels of resistin. OT treatment increased circulating plasma OT levels, significantly reduced serum resistin, body fat accumulation (19%: P <0.001), fasting blood glucose levels (23%: P <0.001), and improved glucose and insulin sensitivity. OT also normalized cardiac OT receptors, ANP and BNP expressions and prevented systolic and diastolic dysfunction as well as cardiomyocytes hypertrophy, fibrosis and apoptosis. Furthermore, OT reduced cardiac oxidative stress and inflammation, and normalized the AMP-activated protein kinase signalling pathway. The complete normalization of cardiac structure and function by OT treatment in db/db mice contrasted with only partial improvement of hyperglycaemia and hyperinsulinaemia. These results indicate that chronic treatment with OT partially improves glucose and fat metabolism, reverses abnormal cardiac structural remodelling, preventing cardiac dysfunction in db/db mice, therefore OT plays a cardio-protective role in the diabetes.

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Novel human resistin antagonist (monomeric C6A mutant) reduced body weight gain and restored insulin responsiveness in mice fed high fat diet
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Resistin promotes both inflammation and insulin resistance associated with energy homeostasis impairment. Resistin is secreted by adipose tissue and macrophages, but its mechanism of action remained unknown because its receptor was not characterised. Recently, we have shown that central resistin acts by way of structural modifications of the TLR4 receptor promoting insulin resistance and reducing insulin sensitivity. Here, we aim to block resistin action in HFD mice that are prone to obesity and inflammation, and attempt to reverse these metabolic disorders. For this purpose, we have developed recombinant human resistin mutant (C6A) that does not form the dimeric molecule of resistin and acts as resistin antagonist (RA). The quality and purity of RA has been verified by SDS-PAGE and SEC analysis. Firstly, we tested the efficacy of RA in human neuronal cells SH-SY5Y and in mouse erythropoietic cell line. We showed that resistin (100 ng/ml) induced the phosphorylation of Akt, while RA had no such activity in both cell lines. Importantly, RA (10 mg/ml) treatment totally abolished resistin-dependent Akt phosphorylation. Once, the efficacy of RA demonstrated, we attempted to reverse the HFD-dependent insulin resistance by RA treatment in vivo. For this purpose, we have fed male C57BL/6 mice with HFD for 6 weeks and then mice received for 14 days daily injection of RA (0.3 mg/day per mice). We clearly show that RA leads to a significant decrease in body weight of HFD mice mainly due to loss of visceral fat. Importantly, RA treatment significantly improved both glucose tolerance and insulin responsiveness of HFD mice. Interestingly, hypothalamic IL6 expression, and reactive gliosis in the arcuate nucleus were markedly reduced in RA-treated HFD mice. Collectively, these findings indicate that the blockade of resistin action reduced body weight gain, visceral fat content and hypothalamic inflammation and restored insulin responsiveness of mice fed high fat diet.

Disclosure
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Stable analogues of the dual agonist dogfish glucagon show better therapeutic potential than exendin-4 in diet induced obese diabetic mice
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Recent acute in vivo studies have shown that structural modifications of dogfish glucagon improves peptide stability and these analogues can act as dual agonists at both glucagon and GIP-1 receptors. Here, we compared the effects of chronic (51 days) twice daily administration of [o-Ala2]dogfish glucagon (Pep-N) and [o-Ala2]dogfish glucagon-exendin-4(31–39) construct (Pep-C), exendin-4(1–39) or saline treated controls on metabolic status in groups (4 x n=8) of male (Swiss TO) diet induced (4 months pre-conditioned on 45% high fat diet) diabetic mice. Non-fasting blood glucose was significantly reduced in all treatment groups vs saline controls after one week and remained lower throughout the remaining study period (P <0.05 to P <0.001). Peptide therapies had no significant effect on cumulative food intake but the increase in body weight gain was lower (P <0.05) following Pep-N and Pep-C administration vs saline treated controls. Plasma insulin concentrations progressively increased (P <0.05 to P <0.01) in all three peptide treated groups vs high fat fed saline treated controls. After day 51, Pep-N and Pep-C showed an improved glycaemic response (0-120 min. area under curve AUC) to i.p. glucose (18 mmol/kg body weight) (P <0.001), along with exendin-4 (P <0.05) compared to saline treated controls. Also a significant
rise in plasma insulin concentration was noted over 120 min within all peptide treatment groups with Pep-C being the most effective insulinotropic peptide (P < 0.001). Following chronic treatment, an insulin sensitivity test (25 U/kg body weight) showed that extendin-4 (P < 0.05) and Pep-C (P < 0.001) had enhanced insulin sensitivity vs saline treated controls. Terminal DEXA scan densitometry analysis revealed that percentage body fat mass was significantly decreased (P < 0.001) in Pep-N and Pep-C treated mice but not following extendin-4 treatment. Pep-C effectively lowered plasma triglyceride concentrations (P < 0.01). Pep-N and Pep-C caused a reduction in the terminal circulating plasma glucagon concentrations (P < 0.01) compared to saline treated controls. Finally, pancreatic insulin content was unchanged in all of the peptide treated groups compared to saline treated control mice. In conclusion, chronic twice daily treatment with the novel dual agonist Pep-C demonstrated improved glycaemic control and lipid profiles compared with extendin-4 therapy in diet induced obese diabetic mice.

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**GP.15.06**

Activation of GPR120 by lipid agonists modulates glucagon secretion in pancreatic islets and improves glucose tolerance in mice

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GPR120 is a rhodopsin-like GPCR that has a high affinity for long-chain saturated fatty acids 14–18 carbons and unsaturated fatty acids 16–22 carbons. The beneficial effects of GPR120 on β-cell function and glucose homeostasis have recently been reported however its role in glucagon secretion is unknown. GPR120 and glucagon expression were examined by double immunohistological studies using a glucagon secreting cell line (β-TC1.9) and pancreatic tissue from normal and high-fat fed (HFF) NIH-Swiss mice. Mechanistic and molecular studies with GPR120 agonists were used to examine alterations in intracellular Ca²⁺ and GPR120 mRNA expression in β-TC1.9 cells. Cytotoxicity was assessed by LDH release. Acute *in-vivo* effects of lipid GPR120 agonists on plasma glucose and insulin hormone levels were assessed in NIH-Swiss mice. Immunocytochemistry demonstrated GPR120 co-localisation with glucagon in mouse pancreatic islets; results were confirmed in β-TC1.9 cells. Histological studies revealed that insulin expression was increased (P < 0.001) in β-TC1.9 cells compared with basal glucagon secretion. In β-TC1.9 cells, GPR120 agonists (0.1 μmol/kg body weight) in glucose tolerance studies were tested in NIH-Swiss mice. DHA and ALA improved glycemia (P < 0.001) whilst synthetic agonist GW-9508 augmented insulin secretion (P < 0.01) by 48% after 15 min and glucagon secretion (P < 0.001) by 67% after 30 min. GPR120 is expressed on pancreatic α cells, and agonists at this receptor modulate glucagon secretion, with therapeutic potential for type-2 diabetes.

**Diabetes and obesity – Clinical obesity and cardiovascular**

**GP.16.01**

Suppression of plasma free fatty acid concentrations similarly reduces myocardial lipid content and left ventricular systolic function in type 2 diabetic patients and healthy controls

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Background Metabolic inflexibility in T2DM might result in reliance on free fatty acids (FFA) as substrates to maintain myocardial energy metabolism compared to lean and healthy controls. Thus, we investigated the effects of an acute suppression of circulating FFA on myocardial lipid content and left ventricular function in extreme phenotypes.

**Methods**

T2DM patients (age: 56 ± 11a; BMI: 28 ± 3.5 kg/m²; HbA1c: 7.29 ± 0.88%) and nine healthy young controls (age: 24 ± 3a; BMI: 24 ± 3.5 kg/m²) were investigated on two study days in random order. At baseline and at 180 min placebo or Acipimox was administered to inhibit adipose tissue lipolysis. Myocardial lipid content (MYCL) and systolic LV function was measured by 1H-magnetic-resonance-spectroscopy and tomography at timepoints I (0–60 min), II (180–240 min) and III (420–480 min).

**Results**

In T2DM and controls Acipimox similarly reduced MYCL significantly (T2DM: −0.39 ± 0.07 vs. CON: −0.39 ± 0.01% compared to baseline), accompanied by a distinct decrease in parameters of LV systolic function without any difference between both groups (EF: −13.2 ± 8 vs. −9.2 ± 7% compared to baseline; cardiac index: −6.2 ± 15 vs. −11 ± 13% compared with baseline; T2DM vs. CON). Baseline MYCL and EF were higher in T2DM compared to controls (MYCL: 0.48 ± 0.12% vs. 0.18 ± 0.01%; P < 0.001; EF: 77.1 ± 1.7% vs. 61 ± 1.2%; P < 0.001; T2DM vs CON). At baseline a strong correlation of MYCL and EF (r = 0.537; P < 0.001) was observed.
Discussion
Pharmacological inhibition of adipose tissue lipolysis reduces MYCL to a similar extent in T2DM and healthy controls. Thus, cardiac lipid stores might be essential for maintaining systolic heart function. These results are of clinical interest, since lipolysis-inhibiting drugs are frequently used in routine care in T2DM (insulin, nicotinic-acids).

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GP.16.02
The effect of omega-3 polyunsaturated fatty acids on the arterial stiffness parameters in patients with T2DM and cardiovascular autonomic neuropathy
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Introduction
The aim of study was to analyse the effect of long-chain polyunsaturated higher ω-3 fatty acids (PUFAs) on the arterial stiffness parameters in patients with type 2 diabetes (T2DM) and cardiovascular autonomic neuropathy (CAN).

Description of methods
The study involved 39 patients with moderate CAN (55.2 ± 3.8 years, HbA1c 7.1 ± 0.5%). The aorta (AIxαao), brachial augmentation index (AIxbr), pulse wave velocity (PWV) were assessed by TensioMedTM Arteriograph 24 (Hungary). Patients with CAN were allocated to two groups: control (n = 18) received standard therapy and treatment (n = 21) received in addition one capsule/day of the ω-3 PUFAs (Δ90%). The duration of the study was 3 months. Statistics: ANOVA.

Results
The arterial stiffness parameters in patients with moderate CAN exceed the physiological values, in particular AIxαao +26.2% (P < 0.01), AIxbr +66.2% (P < 0.001), PWV +24.7% (P < 0.001) compared to patients with T2DM without CAN. Description of methods
Prescription of ω-3 PUFAs was accompanied by more decrease of AIxαao, PWV during the 24 h, decrease of AIxbr, PWV during the day and decrease of AIxαao, AIxbr, PWV during the night. Simultaneously no significant influence on the AIxαao during the active period of day was not found (table).

Table

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Groups</th>
<th>Day/Night</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>% change from baseline</th>
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</thead>
<tbody>
<tr>
<td>AIxαao, %</td>
<td>Control Day</td>
<td>30.4 ± 1.97</td>
<td>28.4 ± 1.68</td>
<td>-4.3 ± 1.76</td>
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<td>Night</td>
<td>33.2 ± 1.98</td>
<td>30.1 ± 1.27</td>
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<tr>
<td>Treatment</td>
<td>Day</td>
<td>30.6 ± 1.32</td>
<td>28.4 ± 1.12</td>
<td>-16.2 ± 3.12</td>
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<tr>
<td></td>
<td>Night</td>
<td>36.6 ± 1.65</td>
<td>31.7 ± 1.23</td>
<td>-11.2 ± 4.2</td>
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<tr>
<td>AIxbr, %</td>
<td>Control Day</td>
<td>-10.6 ± 3.37</td>
<td>-12.0 ± 3.11</td>
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<td>-10.0 ± 17.23</td>
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<tr>
<td>Treatment</td>
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<td>Night</td>
<td>-1.8 ± 2.79</td>
<td>-10.4 ± 2.23</td>
<td>-98.0 ± 18.1</td>
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<tr>
<td>PWV, m/s</td>
<td>Control Day</td>
<td>10.2 ± 0.4</td>
<td>9.6 ± 0.4</td>
<td>-6.0 ± 12.21</td>
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<tr>
<td></td>
<td>Night</td>
<td>10.9 ± 0.4</td>
<td>10.3 ± 0.36</td>
<td>-4.9 ± 1.41</td>
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</tr>
<tr>
<td>Treatment</td>
<td>Day</td>
<td>11.0 ± 0.35</td>
<td>9.7 ± 0.39</td>
<td>-11.2 ± 2.09</td>
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<tr>
<td></td>
<td>Night</td>
<td>11.3 ± 0.48</td>
<td>9.0 ± 0.44</td>
<td>-18.9 ± 3.9</td>
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</table>

Note: The results are given as absolute values and as % change from baseline. (Δ2%, Mean ± SEM); *P < 0.05, **P < 0.01 – compared to baseline.

Conclusion
Therefore, the administration of ω-3 PUFAs for 3 months promotes reduction of artery stiffness parameters in patients with T2DM and CAN.

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GP.16.03
The dipeptidyl peptidase-IV inhibitor (gemigliptin) inhibits the expression of vascular adhesion molecules and inflammatory cytokines in HUVECs via Akt- and AMPK-dependent mechanisms
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Recently, dipeptidyl peptide-IV (DPP-IV) inhibitor, a major anti-hyperglycaemic agent, has received substantial attention as a possible therapeutic target for inflammatory diseases such as atherosclerosis. However, the direct molecular mechanisms through which DPP-IV inhibitor mediates anti-inflammatory effects in vascular endothelial cells have not been clarified. The effects of the DPP-IV inhibitor, gemigliptin, were analysed in human umbilical vein endothelial cells (HUVECs) and THP-1 cells. Using western blotting, we demonstrated that gemigliptin efficiently increased the level of AMP-activated protein kinase (AMPK) and Akt phosphorylation in a dose-dependent manner. The levels of lipopolysaccharide (LPS)-mediated phosphorylated nuclear factor-kB (NF-kB) and c-Jun N-terminal kinase (JNK) were significantly decreased after gemigliptin treatment. Furthermore, gemigliptin reduced LPS-induced expression of adhesion molecules and inflammatory cytokines such as vascular cell adhesion molecule-1 (VCAM-1), E-selectin, tumour necrosis factor-α (TNF-α), monocyte chemotact-tractant protein-1 (MCP-1), interleukin-1β (IL1β), and IL6 in HUVECs. In macrophage-like THP-1 cells, gemigliptin effectively inhibited LPS- and LDL-induced foam cell formation. However, these anti-inflammatory and anti-atherosclerotic effects of gemigliptin in HUVECs and THP-1 cells were significantly reduced after treatment with an AMPK or an Akt inhibitor. Our results suggest that gemigliptin efficiently inhibited LPS-induced pro-inflammatory effects in vascular endothelial cells by attenuating NF-kB and JNK signalling via Akt/AMPK-dependent mechanisms. Therefore, the DPP-IV inhibitor, gemigliptin, may directly protect the vascular endothelium against inflammatory diseases such as atherosclerosis.

Disclosure
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GP.16.04
Nocturnal blood pressure cut off points related to the development of microvascular complications and arterial hypertension in patients with type 1 diabetes
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Introduction
In preliminary results of our group, we detected an association between the mean nocturnal blood pressure and development microvascular complications. The objective was to evaluate possible nocturnal blood pressure cut off points in relation to the development or progression of retinopathy, microalbuminuria and arterial hypertension in type 1 diabetic patients.

Methods
We designed a prospective observational study of 85 patients, clinically normotensive and without microalbuminuria, monitored over 7 years. We performed a 24 h-ambulatory blood pressure monitoring (ABPM) at the beginning and after 7 years. We evaluated the development/progression of retinopathy and development of microalbuminuria and established hypertension over the follow up period. We analyzed different ranges of nocturnal systolic blood pressure (SBP) and diastolic blood pressure (DBP) as independent variables for the development of such complications.

Results:
Of the 85 patients included in the analysis, 55.3% (n=47) were women with an average age of 27.9 ± 6.1 years and a length of disease of 12.3 ± 6.5 years. 69 patients completed 7-year study. After the follow up period, 31.8% presented development/progression of retinopathy, 10.14% developed microalbuminuria and 7.24% of the normotensive patients progressed to established hypertension. Initial nocturnal DBP greater than 65 mmHg showed as a risk factor for the progression of retinopathy and the development of hypertension after 7 years. In spite of the association between the nocturnal SBP and development of microalbuminuria, we did not detect a cut off point from which a significant risk appeared.

Conclusions
In clinically normotensive and normoalbuminuric patients with type 1 diabetes, a nocturnal DBP greater or equal to 65 mmHg is related to the development/progression of retinopathy and the development of established hypertension.

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**GP.16.05**

**Evaluation of cardiovascular risk factors in long-term survivors of brain tumours who received cranial irradiation**

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Introduction

There is strong evidence that adult survivors of childhood cancer have excess premature vascular morbidity and mortality, the pathophysiological mechanism of which remains unresolved.

Methods

We undertook a cross sectional study to assess cardiovascular risk in long-term survivors of brain tumours following cranial irradiation compared with healthy matched controls. The following cardiovascular markers were measured: full lipid profile, fasting glucose and parameters of body composition. Basal anterior pituitary hormone profile and dynamic pituitary tests (ITT or GST) were also undertaken in the patient group.

Results

36 patients (mean age 30.9±13.9 years) and 36 controls (mean age 31.5±13.4 years) were assessed. Evidence of hypopituitarism was present in 91.2% of patients (severe GHD 64.7%, partial GHD 26.5%, LH/FSH deficiency 17.6%, severe ACTH deficiency 8.8%). No significant difference was found in the TSH (P=0.2) and free T4 (P=0.4) values between patients and controls. Total and LDL-cholesterol were significantly higher in patients compared with controls (5.2±1.1 mmol/l vs 4.6±1.0 mmol/l, P=0.007 and 3.1±0.8 mmol/l vs 2.7±0.9 mmol/l, P=0.011 respectively). Body composition analysis showed patients had significantly elevated waist circumference (93.9±15.6 cm vs 80.3±10.9 cm, P<0.001), waist-hip ratio (0.88±0.08 vs 0.82±0.08, P<0.001), fat mass (FM) and FM% (40.8±12.2 kg vs 15.7±6.6 kg, P=0.003 and 29.6±9.7% vs 22.1±8.3%, P<0.001), truncal FM and truncal FM% (13.0±6.7 kg vs 8.2±3.7 kg, P=0.004 and 29.4±10.0% vs 21.0±8.1%, P<0.001) and summative (suprailiac, infrascapular, biceps, triceps) skinfold thickness (75.7±3.2 mm vs 42.5±16.4 mm, P<0.001) when compared with controls. No differences were found in the HDL, triglycerides, glucose, BMI and lean body mass between the two comparison groups.

Conclusion

Our results show that cancer survivors following cranial irradiation demonstrate an adverse lipid and body composition profile, which may contribute to the increased cardiovascular risk of these patients. The high prevalence of hypopituitarism in the patient group may explain at least partially the alterations observed in the cardiovascular risk markers.

**Disclosure**

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**GP.16.07**

**Lipocalin-2 regulates cardiomyocyte autophagy to control apoptosis and insulin sensitivity: importance in heart failure**

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Lipocalin-2 has become an important biomarker for kidney disease and it is important to now understand it’s role in cardiomyopathy and understand it’s direct effects on the heart. Autophagy is now established as a critical determinant of cardiac function and here we investigated regulation of cardiac autophagy by lipocalin-2 and the functional consequences. After treating HEK293 cells with lipocalin-2 we used transmission electron microscopy, Western blotting and immunofluorescence for LC3-II, tandem fluorescent LC3 overexpression and MagicRed assay for lysosomal cathepsin activity to show that lipocalin-2 reduced autophagic flux. Lipocalin-2 also reduced oxidative stress in response to hypoxia. This correlated with reduced insulin sensitivity which was reversed when rapamycin was used to stimulate autophagy. We also observed that lipocalin-2 induced cardiomyocyte apoptosis. Mechanistically, we have shown that lipocalin-2 increased intracellular iron levels to mediate pro-apoptotic effects. We translated these studies to animal models by performing coronary artery ligation surgery to induce ischemia in wildtype and lipocalin-2 knockout mice. Our preliminary data indicates that ischemia-induced caspase-3 and -12 activity was exaggerated in lipocalin-2 knockout versus wildtype. In summary, lipocalin-2 regulates cardiomyocyte autophagy, oxidative stress, apoptosis and insulin sensitivity and the exact physiological significance of these cardiac remodeling effects must now be determined.

**Disclosure**

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**GP.16.06**

**Cardiovascular complications in type 1 diabetic patients**

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Background

Although the issue of cardiovascular complications in type 2 diabetic patients is widely discussed and recommendations for such screening are known, it is less common to do so for type 1 diabetes mellitus (T1DM). Unfortunately, the mortality rate due to vascular complications is higher among type 1 diabetic patients than in the general population.

Patients and methods

Seventy-six patients with T1DM history over 20 years were included in our study. We analysed the occurrence of cardiovascular complications and their risk factors: BMI, HbA1c, lipid profile, hypertension, smoking, alcohol consumption and family history of cardiovascular diseases and diabetes.

Results

A total of 76 patients were enrolled: 43 men and 33 women, the mean age and the mean diabetes duration was 39.9 years ±9.5 (24–61 years) and 28.18±5.9 years respectively. The HbA1c was 10.26±1.76%. Smoking was present in 23.7% of our patients; hypertension was associated in 25.3±4.3% and dyslipidaemia in 11.3±3.18%. The frequency of chronic diabetic complications was as follows: diabetic retinopathy = 75%; peripheral polyneuropathy = 55.3% and nephropathy = 28.9%. 976 patients had cardiovascular complications: among this group eight patients were smoker, seven had a family history of diabetes mellitus and six without nephropathy. Proven stroke was diagnosed in six patients with over 20 years of T1DM history, coronary disease and peripheral arteriopathy were present in three and two patients respectively.

Conclusion

Beyond 20 years of diabetes history, cardiovascular complications dominate the prognosis.

**Disclosure**

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**GP.16.08**

**Vascular and cardiac function in young adults with classical congenital adrenal hyperplasia**

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Background

The patients with classical congenital adrenal hyperplasia (CAH) have increased cardiovascular risk due to the lifelong glucocorticoid therapy and the disease per se.

Objective

To evaluate vascular and cardiac function in adults with CAH during optimal corticosteroid and fludrocortisone replacement therapy.

Patients and methods

Cross-sectional study of 19 adults with CAH (age 23.7 years ±3.8; males 63%) compared to 21 healthy voluntaries (age 23.2 years ±2.6; males 60%) matching to the age and BMI. All of the participants had assessed the flow mediated
dilatation of the brachial artery (FMD), the intima-media thickness of the common carotid artery (CIMT), the intima-media thickness of the common femoral artery (FMD%), left ventricular mass index (LVMII) and longitudinal left ventricular function using two-dimensional speckle-tracking echocardiography (LSTE). Classical cardiovascular risk factors and hormones status were also measured.

Results
The patients with CAH compared with controls had decreased FMD (mean FMD% 9.4, 95% CI: 7.2–11.6 vs mean 19.8, 95% CI: 17.7–21.9; P < 0.01) and the difference was still significant after correction for potential confounders such as: brachial artery diameter, age, sex, the dose of corticosteroid and fludrocortisone (mean FMD% after correction 9.2, 95% CI: 4.2–14.3 vs 20.0, 95% CI: 15.2–24.9; P = 0.02). The CIMT and FIMT was higher in the CAH group baseline (for CIMT mean 0.47 mm, 95% CI: 0.46–0.49 vs mean 0.40 mm, 95% CI: 0.38–0.42; P < 0.001, for FIMT mean 0.47 mm, 95% CI: 0.45–0.48 vs mean 0.41 mm 95% CI: 0.38–0.42; P < 0.001) but not after correction for potential confounders such as: age, sex, the dose of corticosteroid and fludrocortisone, total cholesterol level, smoking status (for CIMT P = 0.44, for FIMT P = 0.12). The CAH subjects compared with controls have normal and similar LVEF%, LVMI. The mean absolute value of LSTE differs in the CAH patients compared with controls (20.9%, 95% CI: 20.2–21.6 vs 21.9%, 95% CI: 21.2–22.5; P = 0.03).

Conclusions
Young adults with CAH have impaired endothelial function but the increased of IMT may be related to hormones supplementation. In addition patients with CAH have impaired left ventricular function in two-dimensional speckle-tracking echocardiography.

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Pituitary – Neuroendocrinology and central salt regulation

GP.17.01
Reticine acid increases glucocorticoid receptor phosphorylation via cyclin-dependent kinase 5
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Background
According to the literature, glucocorticoid receptor (GR) function is modulated by phosphorylation. Reticine acid (RA) can activate some cytoplasmin kinases able to phosphorylate GR.

Aim
As RA and glucocorticoids interact in neuronal cells, we investigated whether RA could modulate GR phosphorylation in such cells.

Methods
HT-22 hippocampal cells were cultured 4d with or without dexamethasone (Dex, 10-6 M) or RA (10-6 M). Western blots were either performed on total cell extracts or cytosolic and nuclear fractions.

Results
Indeed, a 4 d treatment by RA decreased the nuclear expression of GR phosphorylated on Serine 220 (pSer220GR). Conversely, RA increased Dex-dependent nuclear pSer220GR expression in HT22 cells. This treatment by RA had no effect on cyclin-dependent kinase 5 (CDK5) expression but increased the expression of p35 a major CDK5 cofactor. In the nucleus, roscovitine, a CDK5 inhibitor, suppressed the RA-dependent increase of the Dex-induced pSer220GR expression. Furthermore, roscovitine altered RA-dependent decrease of GR-induced transcriptional activity when using either a reporter gene with GR response elements or GR sensitive genes such as BDNF or tissue transglutaminase.

Conclusion
This study demonstrates that RA modulates GC signalling by increasing Ser220GR phosphorylation through at least a modulation of CDK5/p35 activity with an increase of cytoplasmin p35/p25 ratio. This study supports the idea that GR phosphorylation depends on the cellular environment aside from the presence of GR ligands.

Disclosure
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GP.17.02
Glp-l regulates the reproductive function and synchronizes the onset of the puberty in female rats
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Glp-l is a gut hormones with insulotrophic effects. Glp-l is expressed at the hypothalamus having regulatory functions in food intake and neuroendocrine corticovasal axis (HPA). Energy balance and HPA have deep influence in the gonadal function of mammals. Exendin-4 (Ex4) is a potent agonist for the GLP-1 receptor.

Objectives
To evaluate the effects of native GLP-1 (7–36)-NH2(GLP-1) and Ex4 in the function of the reproductive system in adulthood and onset of puberty in female rats.

Methods
Adult female rats were ivc injected with a single dose of GLP-1/Ex4 or vehicle (Veh) in the morning of proestrous. Blood samples were taken by jugular venipuncture at different stages of the subsequent estrous cycle. Ovaries were isolated for histological studies. Another group of females was housed with males for mating that confirmed by sperm-positive vaginal plug. The dams were sacrificed by decapitation after delivery, and number of undelivered but implanted fetuses and neonates born were counted and weighed. Prepubertal rats were treatment with GLP-1/Ex4/Veh and monitoring of body weight, intake, vaginal opening (VO) and hormone levels was done.

Results
GLP-1 administration in the morning of proestrus doubled the amplitude of preovulatory LH surge and modified the estradiol and progesterone levels along the estrous cycle. That promoted a marked increase in number of Graafian follicles and corpora lutea, and consequently in litter size. Conversely, Ex4 produced a partial blockade of preovulatory LH surge, yet not affecting the number of mature follicles or corpora lutea. Administration of low doses of GLP-1 to pre-pubertal rats synchronized vaginal opening and increased LH levels. By contrast, chronic exposure to Exendin-4 produced a significant reduction in LH and complete blockade of puberty onset.

Conclusions
GLP-1 increases the preovulatory surge of gonadotropins and ovulation rate in adulthood and synchronise the onset of puberty. These effects were not reproduced by Ex4.

Disclosure
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GP.17.03
Insulin-induced hypoglycaemia decreases IGF1 bioactivity in humans: a missing link to increased mortality in diabetic patients?
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Insulin-induced hypoglycaemia decreases IGF1 bioactivity in humans: a missing link to increased mortality in diabetic patients?

Background
The mechanisms underlying the association between severe hypoglycaemia and increased cardiovascular mortality among patients with diabetes mellitus are not...
fully understood. Our aim was to evaluate changes in GH/IGF1 axis during insulin-induced hypoglycaemia, as a possible link.

Methods

Twenty-five healthy subjects, 12 obese participants (OP: 6/6; 34.4 ± 1.7 kg/m²), and 13 healthy lean participants (LP: 6/7; 21.7 ± 0.6 kg/m²) were studied using insulin tolerance test and changes in GH, total IGF1, IGF binding proteins (IGFBPs) and IGF1 bioactivity, measured by the cell-based KIRA method, were investigated. Moreover, the effect of insulin on mRNA expression of parts of the GH/IGF1 system was further studied in mouse primary hepatocytes.

Results

Under hypoglycaemic conditions, insulin significantly increased IGFBP2 and decreased IGFB1 bioactivity in both groups (P < 0.01). This was followed by a surge in GH (P < 0.01). As expected, insulin increased IGFBP1 levels, whereas no changes in total IGF1 and IGFBP3 levels were observed. In vitro, insulin stimulation of primary hepatocytes lead to a decrease of IGFBP1 and IGFBP3 and increase of IGFBP2 mRNA expression.

Conclusion

The insulin-induced hypoglycaemia is associated with a decrease in IGFB1 bioactivity through up-regulation of IGFBP2. Our results point to a possible and previously poorly explored mechanism explaining the strong association between hypoglycaemia and increased cardiovascular mortality among diabetic patients.

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GP.17.04

Copeptin reflects thermal strain during exercise in a hot environment

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Background

Exertional heat illness (EHI) is an incapacitating and sometimes fatal phenomenon. It is associated with elevated core temperature (Tc), and the systemic inflammatory response syndrome. EHI-preventive guidelines recommend maintaining Tc ≤ 38 °C, an important thermoregulatory threshold above which vasomotor compensation plateaus and pronounced excursions in key pituitary and adrenal hormones occur. Copeptin, the C-terminal part of the vasopressin (AVP) precursor peptide, can be assayed as a surrogate for AVP. Copeptin shows prognostic potential in a range of inflammatory and cardiovascular conditions but its relationship with Tc has not been characterised.

Objective

To investigate the serum copeptin response to Tc changes during exercise in a hot environment.

Methods

15 subjects from a British Army infantry battalion were studied on their sixth day in Kenya during a 4.5 h simulated combat assault exercise. Tc was recorded by telemetry from ingested pills every 60 s during the exercise. Serum copeptin was assayed pre- and post-exercise.

Results

Tc increased in 15/15 subjects. Average Tc (TcAv) was 37.36 ± 0.21 °C. Change in plasma copeptin concentration (∆copeptin) was positive in 13/15 subjects. Mean ∆copeptin was 6.67 ± 5.83 pmol/l (P = 0.0006). In eight subjects with maximum Tc (TcMax) > 38 °C, mean ∆copeptin was more than 400% greater than for the seven subjects with TcMax < 38 °C (10.40 ± 4.34 pmol/l vs 2.40 ± 4.2 pmol/l; P = 0.0059). There was a strong positive correlation between TcAv and ∆copeptin (r = 0.75, P < 0.01).

Conclusions

Copeptin stratified military subjects relative to the critical thermal threshold of 38 °C. Copeptin may be a plausible biomarker of thermal strain and EHI risk in both military and civilian populations.

Disclosure

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GP.17.05

Hypernatremia and copeptin levels in the elderly hospitalised patient

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Introduction/objective

Elderly patients have a higher prevalence of hypernatremia. Previous studies suggested that impaired ADH secretion contributes to development of hypernatremia in the elderly. Copeptin is the C terminal part of the ADH precursor and is more stable in plasma than ADH. The aim of this study was to detect demographic and clinical characteristics of the elderly hypernatremic patient hospitalized in the internal medicine ward, and to increase the understanding of the role of ADH secretion in the pathogenesis of hypernatremia.

Design

Case-control study.

Setting

Internal Medicine ward in a University affiliated hospital.

Participants

33 hypernatremic patients (admission sodium > 150 meq/l, age > 70) compared to 34 normonatremic patients.

Measurements

Demographic, functional and clinical data (APACHE II score) were collected at admission. Serum copeptin levels were obtained 48 hours from admission. Mortality and change in the functional status were followed up to 30 days after discharge.

Results

Patients with hypernatremia presented with significantly lower baseline functional and cognitive states and higher APACHE II score (21.3 ± 8.6 vs 15.4 ± 6.7; P < 0.01). Dementia was present in 97% of the hypernatremic patients compared to 46% of the control group (P < 0.001). Mortality within 30 days of discharge was higher in the hypernatremic group (58% vs 32%, P < 0.05). Higher Copeptin levels were found in the hypernatremic group compared to the normonatremic group (100.2 ± 60.6 pmol/l vs 66.5 ± 57.2 pmol/l; P < 0.05). High levels of Copeptin were associated with higher in hospital (P < 0.05) and 30 days mortality (P < 0.01). Sodium levels were found to correlate with Copeptin levels; yet, an even stronger correlation was demonstrated between Copeptin levels and APACHE II score (r = 0.52, P < 0.001).

Conclusions

Hypernatremia in the elderly at admission is associated with a high rate of mortality. Copeptin is appropriately secreted by the elderly patient with dementia and seems to be a good single disease severity marker.

Disclosure

Mirski fund.

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GP.17.06

Predictors of response to fluid restriction in hyponatremic patients due to the syndrome of inappropriate antidiuresis

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Introduction

Fluid restriction (FR) is often the recommended first-line treatment for hyponatremia due to the syndrome of inappropriate antidiuresis (SIAD). However, FR not always leads to successful correction of hyponatremia, making predictive markers of treatment response desirable. The aim of this study was to
evaluate routinely measured laboratory parameters, copeptin and pro-atrial natriuretic peptide (pro-ANP) as possible predictors of treatment success to FR. Methods and design
We analysed 106 patients with SIAD out of 298 prospectively observed patients with profound hyponatremia (serum sodium < 125 mmol/l). 82/106 patients with SIAD were initially treated with FR and included in this study. FR was defined as a total daily intake of < 1000 ml. According to the change from baseline to follow-up serum sodium (within 24 h), we classified patients into FR responders (increase of > 3 mmol/l) or FR non-responders (≤ 3 mmol/l). We performed regression models to look for correlations between different urine and serum parameters and treatment response.

Results
Of the 82 patients (mean age 67.6 years, 64.6% females) 48 (58.5%) responded to the initial trial of FR. Both baseline levels of urinary sodium and u-osmolality showed a significant correlation with treatment response (P for interaction = 0.004 and P = 0.041 respectively), whereas high levels indicate a FR failure. Initial serum sodium did not predict response to FR (P = 0.26). Similarly, levels of copeptin – a surrogate marker of arginine vasopressin (AVP) – did not reveal a significant correlation with treatment success (P = 0.68). Finally, we found a predictive value of pro-ANP, the higher pro-ANP levels the greater the likelihood of a positive response (P for interaction = 0.004).

Conclusion
Easy measured urinary parameters and pro-ANP correlate with therapeutic success of fluid restriction and may enhance the management of patients with hyponatremia due to SIAD.

Disclosure
Thermo Scientific Biomarkers provided all the kits for measurement of Copeptin and MR-proANP analysis. P Schütz, B Müller, and M Christ-Crain have received speaker honoraria from Thermo Scientific Biomarkers. N Nigro was supported by a grant from the University Basel, Switzerland.

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**GP.17.07**

**Heterogenous patterns of recovery from adipsic diabetes insipidus in adult patients**

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**Introduction**
The natural history of adipsic diabetes insipidus (ADI) is not completely understood. Isolated case reports suggest occasional recovery of adipsia. We present the follow up of a cohort of 12 patients with ADI.

**Setting**
National pituitary unit with interest in diabetes insipidus.

**Methods**
ADI was identified by demonstrating absent thirst and AVP responses to hypertonic saline infusion. Results 12 patients with ADI were identified (five with craniohypophyseal, four with ACOM aneurysm repair, one congenital, one prolactinoma). Three patients died. Six patients had permanent adipsic diabetes insipidus. Three patients had recovery of thirst, with a heterogenous pattern of recovery.

**Case 1**: A 41-year-old female with an intrasellar craniohypophyseal developed postoperative ADI with persistent hyponatraemia (147–172 mmol/l). Two years postoperatively, she complained of thirst, and hypertonic saline infusion showed normal thirst but absent AVP responses, confirming recovery of thirst with persistent DI.

**Case 2**: A 29-year-old Caucasian had craniotomy and radiotherapy for craniohypophyseal which had previously presented with chronic headache and bitemporal hemianopia and developed ADI postoperatively. Eight years post-op, she presented with thirst, seizures and pNa of 112 mmol/l. Hypertonic saline infusion showed persistent DI but thirst responses typical of compulsive water drinking; she has had recurrent hyponatraemia since then.

**Case 3**: A 51-year-old gentleman developed ADI after clamping of an ACOM aneurysm and was treated with desmopressin and sliding fluid scale. 10 years post surgery; he sensed the return of thirst; repeated hypertonic saline infusion showed recovery of both thirst and AVP secretion. He is asymptomatic off desmopressin.

**Conclusion**
We report that three out of 12 patients with ADI recovered thirst after longstanding adipsia. The pattern of recovery was heterogeneous and included complete recovery of ADI, recovery of adipsia only and conversion of adipsia to polydipsia. Both the mortality of 25% and the recovery rate of 25% should be considered during long-term surveillance.

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**GP.17.08**

**A study of hyponatraemia in acute medical admissions**

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**Introduction**
Hyponatraemia is the commonest electrolyte disorder in clinical practice and is closely associated with increased morbidity, mortality and length of hospital stay. It can be classified into mild (124–134 mmol/l), moderate (115–124 mmol/l), and severe (<115 mmol/l). The aim of the study was to determine the prevalence, aetiology, and management of hyponatraemia in general hospital.

**Methods**
A total of 4139 acute medical admissions were studied. Hyponatraemia was found in 536 patients with 441 being mild, 86 moderate and nine severe; 130 cases were analysed further in details.

**Results**
Out of 130 cases; 86 were of mild (66%), 42 moderate (32%), and one severe hyponatraemia (0.8%). The mean age was 75.1 years (17–99) and there is equal male to female ratio. The cause of hyponatraemia was only identified in 68% with diuretics accounting for 41 (46%), Syndrome of Inappropriate ADH Secretion (SIADH) for 36 (40%) and fluid overload for 12 (9%) of cases. The treatment of hyponatraemia included intravenous fluid resuscitation in 52, cessation of diuretics in 43 and fluid restriction in 48 of cases. One subject with severe hyponatraemia received demeclocycline, none of the subjects received hypertonic saline or Vasopressin receptor antagonist. While the average length of stay for all medical admissions was 4 days, the average length of stay is 17.1 days (2–70) in those with hyponatraemia.

**Conclusion**
Hyponatraemia, which presents in 12.9% of our admissions, is associated with significantly prolonged hospital length of stay. The use of diuretics and SIADH were the main cause of hyponatraemia in our cohort. Our study highlighted the challenge in the diagnosis as evidenced by 32% of patients in whom diagnosis was not reached. A trust guideline has been developed as a response to this issue.

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**GP.17.09**

**The dopastatim BIM-23A760 distinctly influences key functional endpoints in different types of pituitary adenomas and normal pituitaries: role of somatostatin and dopamine receptor profile**

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**Introduction**
Hyponatraemia, which presents in 12.9% of our admissions, is associated with significantly prolonged hospital length of stay. The use of diuretics and SIADH were the main cause of hyponatraemia in our cohort. Our study highlighted the challenge in the diagnosis as evidenced by 32% of patients in whom diagnosis was not reached. A trust guideline has been developed as a response to this issue.

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Chimeric somatostatin (SST)/dopamine (DA) compounds, termed dopastatins, such as BIM-23A760, an agonist for SST (st2 and st5) and DA (D2) receptors, are emerging as promising new approaches to treat pituitary adenomas. However, their actions and mechanisms on the different types of pituitary tumours are still incompletely understood. Thus, the aim of this study was to analyse a set of key functional parameters (signaling pathways, hormonal expression and secretion, cell viability, and apoptosis), in response to BIM-23A760 in a series of 74 human pituitary tumours: 22 somatotropinomas, five mixed GH/PRL-secreting adenomas, 11 corticotropinomas, 26 NFPAs, six prolactinomas, one FSH-secreting gonadotropinoma and three TSH-omas; and in five normal human pituitaries and pituitary samples derived from three female olive baboons (Papio anubis). Although, BIM-23A760 has recently been withdrawn from clinical development after finding that a dopaminergic metabolite accumulates and interferes with the activity of the parent compound in vivo, it is still considered a good prototype molecule for dopastatins, and the results generated herein might be indeed useful in understanding and predicting the response to this type of compounds, which may be used for clinical purposes in the future. Our results demonstrate that BIM-23A760 differentially impacted all functional parameters analysed, with most responses being clearly inhibitory for cell signalling, hormone secretion and cell survival. Yet, interestingly, certain pituitary adenomas displayed distinct, even opposite responses to BIM-23A760 (i.e. paradoxical stimulatory responses), which were associated with the relative expression levels of SST- and DA-receptors. In particular, alterations on the expression of st5 and its truncated variant, st5TM/2, might represent potential molecular signatures contributing to the differential, inhibitory/stimulatory response to BIM-23A760 in GH- and ACTH-secreting adenomas. Altogether, our results reinforce the notion that chimeric dopastatins (e.g. BIM-23A760) can affect multiple, clinically relevant parameters on most types of pituitary adenomas and may represent new therapeutic tools to treat pituitary tumours, wherein the relative SST/DA receptor expression profile might provide useful molecular markers to predict the ultimate response of these tumours to BIM-23A760.

**Disclosure**

This work was supported by Junta de Andalucía (CTS-1406, BIO-0139, PI-0639-2012) Ministerio de Economía y Competitividad, Gobierno de España (BFU2013-43282-R), Instituto de Salud Carlos III (PI13/00651), Centro de Investigación Biomédica en Red de la Fisiopatología de la Obesidad y Nutrición (CIBERObn) and Ayuda Merck Sero 2013. M D Culler is an employee of IPSEN.

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**GP.18.02**

**Neuroactive steroids as predictive markers for Alzheimer’s disease**

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**Background and aims**

Neuroactive steroids and their metabolites play an important regulatory role in the nervous system affecting the neuronal plasticity, stress response, learning, and memory. The aim of the study was to compare the steroid metabolome in AD patients and controls.

**Materials and methods**

The study comprised of 48 AD patients (30 women and 18 men; age 73.8 ± 9.54 years) and 33 matched controls (22 women and 11 men; age 68.2 ± 5.94 years). All subjects underwent neuropsychological examination and magnetic resonance imaging of the brain. Biochemical characterisation included examination of fasting glucose and lipid metabolism and the determination of extended spectrum of steroid hormones by GC–MS method (38 steroids and their sulfates). Statistical analyses were performed using Statgraphics Centurion XVI 16.0.07 Software.

**Results**

AD patients had significantly higher insulin secretion (fasting insulin, HOMAIF) and lower CP peptide/insulin ratio compared to controls which indicates the decreased hepatic insulin extraction. AD patients had higher C21 steroids (5α-pregnan-3α, 20α-diol conjugate, women in addition conjugates of androsterone, epitandrosterone, epitetcholanolone, and 5β-androstan-3β, 17β-diol conjugate, women in addition conjugates of androsterone, epitandrost-
GP.18.03

Regulation of sexually dimorphic growth of murine skeletal muscle by Stat5a and Stat5b
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GH regulates IGF1 predominantly through the intracellular signalers Stat5a and Stat5b. Inactivating mutations of Stat5b in humans result in severe growth retardation and low circulating IGF1 concentrations in males and females. In mice, however, there is only a loss of sexually dimorphic growth in males when Stat5b is deleted. No study has observed Stat5b/−/− mice beyond 12 weeks or investigated any subsequent changes in skeletal muscle mass or IGF1 expression. Blood and hindlimb muscles of male and female Stat5b/−/− mice and WT littermates were collected at 6, 12, and 24 weeks of age (n = 16/time and sex). Plasma IGF1 and IGF1 protein concentrations were determined by ELISA and muscle mass was normalised to bone length. C2C12 myoblast cell lines were treated with viral Stat5b siRNA and/or Stat5a siRNA or a scrambled vector (control), then differentiated and treated with GH (100 ng/ml) for 24 h. RNA was harvested for quantitative PCR. The treated cell lines were also treated for 6 h with GH (100 ng/ml) and differentiation was assessed by immunocytochemistry. Sexual dimorphism was reduced, but persisted in Stat5b/−/− mice. Nasaional length, tibia length and normalised hindlimb muscle mass were decreased to a greater extent in male (23%) than in female (14%) Stat5b/−/− mice at all ages (P < 0.001). Concentrations of IGF1 in plasma and skeletal muscle were significantly reduced in male Stat5b/−/− mice at all ages and in female Stat5b/−/− mice after 8 weeks. Stat5a knockdown increased IGF1 mRNA by 35% to a lesser extent than Stat5b or dual Stat5a/5b knockdown (80%) (P < 0.001). Either Stat5a or Stat5b knockdown prevented the GH-induced myocyte hypertrophy, but only Stat5a knockdown blocked the upregulation of IGF1 mRNA by GH. We conclude that both Stat5a and Stat5b have independent roles in GH signaling in murine skeletal muscle.

Disclosure
Waikato Medical Research Foundation (grant number 223).
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GP.18.04

A small hypothalamic volume correlates with impaired cognitive outcome in childhood onset craniopharyngioma on long-term follow up
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Background
Hypothalamic damage caused by craniopharyngioma (CP) is related to memory deficits, disturbed attention, and impaired processing speed. This is the first study that aims to establish a structure to function relationship by assessing cognitive function in adult patients with childhood-onset (CO-CP) along with volumetric analysis of the hypothalamus.

Method
Forty-one (24 women) surgically treated CO-CP patients (median age at diagnosis; 11 years) from the South Medical Region of Sweden were included in the study. Eighteen patients had received cranial radiotherapy. Twenty-eight patients had panhypopituitarism, 35 were treated with ADH and 32 with GH. Time since first operation was 23 years (range 4–49) and median age at investigation was 35 years. Hypothalamic damage was found in 23 patients. All subjects were examined with a battery of cognitive tests and 35 patients underwent magnetic resonance imaging (MRI). A novel delineation procedure based on T1-weighted MRI and landmarks used in histologically processed postmortem hypothalamic tissue was used to estimate hypothalamic volume. Comparisons were made with 32 healthy matched controls.

Results
CP patients with hypothalamic damage (n = 23) had lower cognitive performance pertaining to vocabulary (P = 0.02) short term memory (P = 0.04 and P = 0.01), spatial ability (P = 0.02), and executive functions (P = 0.01 and P = 0.02). A significantly positive correlation was found between the tests of vocabulary (r = 0.352, P = 0.04) and short term memory (r = 0.354, P = 0.04), (r = 0.357, P = 0.04) and hypothalamic volume.

Conclusion
Adults with hypothalamic damage due to CO-CP have impaired memory, spatial ability and executive function. Patients with smaller hypothalamic volume have worse cognitive outcome. To be able to preserve hypothalamic function we need tailored surgical and radiation strategies. Long-term follow up should include training programs pertaining to impaired cognitive function.

Disclosure
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GP.18.05

Presence and functional actions of In1-ghrelin splicing variant reveals a potentially relevant pathophysiological role in human pituitary adenomas
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Pituitary adenomas comprise a heterogeneous group of tumours causing serious comorbidities, which would benefit from identification of novel, common molecular/cellular biomarkers and therapeutic targets. The ghrelin system comprises a complex molecular family with multiple functions, and some of its components have been linked to development of various endocrine-related cancers. In this work we aim at better delineating the patho-physiological significance of the ghrelin regulatory system in pituitary tumours, by pursuing two specific objectives: i) to analyse the presence in pituitary tumours of key components of the ghrelin system: native-ghrelin, the recently discovered splicing variant In1-ghrelin, ghrelin receptors GHS-R1a (full-length) and GHS-R1b (truncated variant), and MBOAT4 (GOAT), the enzyme responsible for ghrelin acylation and ii) to compare the direct effects of native-ghrelin and In1-ghrelin variant administration on selected functional parameters in cell cultures derived from the main types of pituitary adenomas. To this end, we studied a large series of 180 pituitary samples: 76 somatotropinomas, 57 non-functioning pituitary adenomas, 29 corticotropinomas, seven prolactinomas, and 11 normal pituitary samples. The results obtained revealed that expression pattern of ghrelin system components undergoes a striking alteration in pituitary adenomas, as compared with normal pituitary, particularly In1-ghrelin, which was consistently over-expressed in all human pituitary adenoma subtypes. Interestingly, similar to that observed for native-ghrelin, In1-ghrelin was functionally active in cultured pituitary adenoma cells, as it increased GH and ACTH secretion, Ca2+ and ERK1/2 signalling, and cell viability, being the effects of In1-ghrelin variants generally greater than those evoked by native-ghrelin. Finally, overexpression of In1-ghrelin (by transfection using an specific expression plasmid) increased cell viability, while the use of a specific siRNA for this ghrelin variant reduced cell viability. Altogether, our results indicate that ghrelin system components are present and markedly altered in human pituitary tumours, where In1-ghrelin variant, particularly, could play a relevant functional role in the regulation of adenoma pathology, this paving the way for using In1-ghrelin variant as a new tool to explore novel diagnostic/prognostic biomarkers and/or therapeutic targets in these human tumours.

Disclosure
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GP.18.06
Comparison of high-throughput platforms in evaluation of whole genome miRNA expression profiles in pituitary tissues
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Introduction
There are three principal high-throughput methods that have been widely used to determine whole genome miRNA expression profiles: i) microarrays, ii) qPCR based arrays, and iii) next generation sequencing (NGS). Our aim was to compare the results obtained from these platforms in normal and adenomatous pituitary samples and to validate the results by an independent sample set using qPCR.

Material and methods
Using four normal pituitary (NP) and eight non-functioning pituitary adenoma (NFPAs) samples we determined miRNA expression profile by GeneChip microRNA Galaxy Array v1, SOLiD NGS and qPCR based TaqMan Low Density Array Card (TLDA). For biological confirmation expression of 22 miRNAs by individual TaqMan assays on additional 24 NFPAs and ten NPs was used as validation cohort.

Results
Totally 848 miRNAs of which only 162 were detected by all three approaches. Significant but not strong correlations between microarray and NGS (R²: 0.471 and 0.220; P < 0.01), microarray and TLDA (R²: 0.462 and 0.339; P < 0.01), and NGS and TLDA (R²: 0.335 and 0.290; P < 0.01) were detected in NFPAs and NPs respectively. Various bioinformatics, including commercially available software CLCbio, free, web based (Bowtie) and one or our own algorithms were used in order to test whether the different evaluation of NGS data would affect the correlations. Correlations between different bioinformatical approaches were strong (R²: 0.96–0.99) suggesting that these algorithms are useful and give similar results.

Biological validation showed that 81% of TLDA results, and 72% of both microarray and NGS results could be validated regarding the direction of expression changes.

Conclusion
miRNA expression profiles measured by different platforms showed poor correlation and they were hardly comparable. Consequently, selection of screening method can influence experimental results obtained by analyses using high-throughput data (e.g. pathway analysis). However, individual miRNA expression from microarrays and NGS results were replicable in an acceptable percentage by qPCR.

Disclosure
KTIÁ-201200010.

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GP.18.07
The hypothyroidism alters circadian clock expression in anterior pituitary gland
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The anterior pituitary gland occupies a central position in the hypothalamus–pituitary glands axes and secretes hormones involved in reproduction, growth, and metabolism. The plasma concentrations of pituitary hormones present fluctuations during the 24 h and are markedly altered during the hypothyroidism. The presence of an intra-pituitary circadian oscillator might be related to these oscillations; however, the molecular mechanism and the consequences of the hypothyroidism are still unknown. The purpose of the present study was to investigate the expression of Bmal1, Per2, Dpy, Nr1d1, Rora, and Dio2 in pituitary during the adult hypothyroidism. For this, euthyroid and thyroidectomized (Tx) male Wistar rats were euthanized during 24 h, every 6 h. The pituitaries were excised and the mRNA expression was evaluated by RT-qPCR. Geop1 and Rplp0 were used 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, Dpy, Nr1d1, Rora, and Dio2 presented a circadian pattern in anterior pituitary of euthyroid rats, and the peak of Per2, Dpy, Rora, and Dio2 expression occurred at ZT 12, while for Bmal1 was ZT 0/24. In the hypothyroid animals, the circadian pattern of Bmal1, Rora, and Dio2 was lost and the acrophase of Per2, Dpy, and Nr1d1 was advanced about 2.5 h, 3 h, and 45 min respectively. Tx also reduced Messor values of Dpy and Nr1d1. Our studies reveal that the expression of core clock and clock-controlled genes in anterior pituitary gland are changed during the hypothyroidism and might contribute directly or indirectly to the altered hormonal pattern of secretion observed in this pathological condition. Further studies are in progress to assess this issue.

Disclosure
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GP.18.08
Role of miR-375 in onco genesis of pituitary adenomas
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Purpose
MicroRNAs (miRNAs) are a fundamental component of gene regulation mechanisms. Presently, altered miRNA patterns of expression have been documented in different human cancers, and they may explain the distinct behavior of pituitary adenomas (PA) and the differences between subtypes. miR-375 can target among other genes to IGF1 receptor (IGF1R) and participates in reprogramming cancer cell metabolism. The aim of this study was to assess the miR-375 role on pathogenesis of different PA subtypes.

Methods
In this cross-sectional descriptive study, we evaluated miR-375 by qRT-PCR analysis on 60 human PA samples: 29 gonadotrophs (GT), 15 somatotrophs (ST), 8 functioning corticotroph (CT), and eight silent corticotroph adenomas (SCA). Nine healthy pituitary from autopsies were used as calibrator reference. Aggressiveness was graded according to invasiveness (Hardy’s grade IV) and Ki-67 gene expression (> 2.59 fold change (FC)).

Results
In our whole sample miR-375 was associated with sex (men: 3.00 (1.63–4.36) FC values vs women: 1.35 (0.47–1.92) FC values, P = 0.002) and was positively correlated with age (r = 0.466, P = 0.000). miR-375 expression patterns differed depending on PA subtype (P = 0.000) and non functioning PA (GT and SCA) revealed overexpression compared with functioning PA (CT and ST) (81.3 (26/37) vs 39.3 (11/23)), entailed a risk of 6.7 (2.1–21.5) times higher (P = 0.001). Its expression was also correlated with tumor maximum diameter (r = 0.303, P = 0.022) and associated with their extension (intrassell: 1.05 (0.47–1.47); extrassell: 2.50 (1.47–4.39); and invasive: 2.50 (1.07–3.88); P = 0.008). In addition, 66.7% tumors with high or medium aggressiveness grades overexpressed miR-375 vs 28.6% with low grade, which entailed a risk 5.0 (1.6–16.0) times higher (P = 0.005).

Conclusion
Our results revealed a different role for miR-375 in the pathogenesis of PA depending on subtype. This miRNA may be a marker of aggressiveness, but further studies are needed for endorse this utility.

Disclosure
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Molecular classification of pituitary adenomas

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Endocrine Abstracts

Fibrinogen, antithrombin 3, and platelet function analysis in patients with Acromegaly is associated with increased cardiovascular morbidity and mortality. Coagulation parameters and platelet function analysis in patients with Acromegaly were performed to evaluate the involvement of coagulation parameters in acromegaly.

GP.19.01

Pituitary – Acromegaly

GP.18.09

Molecular classification of pituitary adenomas

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Molecular classification of pituitary adenomas

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associated with age at diagnosis ($r^2$: 0.36, $P = 0.02$). LS-BMD and FT-BMD were related to alteration of glucose metabolism ($r^2$: 0.25, $P = 0.04$ and $r^2$: 0.49, $P = 0.002$ respectively).

Conclusions
Acromegalic patients had impaired bone quality despite normal bone density. Further larger studies are needed to define TBS role in fracture risk in acromegaly.

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**GP.19.03**

**Perceived quality of life in acromegaly: results from a tertiary UK centre**

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Introduction
Patients with acromegaly are frequently left with long-term adverse sequelae. When compared with individuals with other pituitary adenomas, patients with acromegaly demonstrate greater impairment in their quality of life (QoL).

Methods
The disease-specific questionnaire, AcroQoL, and the generic psychological general well-being schedule (PGWBS) were used to evaluate QoL in an acromegaly patient cohort. Longitudinal data were also collected to determine change in QoL over a 5-year period.

Results
Baseline responses were collected from 58 patients (age 55.1 ± 13.0 years). For the entire cohort, mean GH and IGF1 values at baseline were 1.53 ± 2.07 µg/l and 102.1 ± 51% of the upper limit of normal (ULN) respectively. Mean duration of GH control (GH < 2 µg/l) was 5.4 ± 4.8 years, whereas for IGF1 this was 4.4 ± 4.3 years. Follow-up responses were obtained from 23 patients (age 55.6 ± 10.0 years). For this subgroup, mean GH and IGF1 at follow-up were 0.76 ± 0.75 µg/l and 110.4 ± 54.3% of ULN respectively (vs 1.6 ± 2.4 µg/l and 110.5 ± 64.7% of ULN at baseline). The mean total score for AcroQoL at baseline was 67.8 ± 18.4 (48.0%). The domain of appearance was the most under-marked, while the highest scores were noted in the personal relationships domain. For the subgroup of 23 patients, no significant difference was found in the baseline and follow-up AcroQoL scores (64.2 vs 65.7, $P = 0.75$). PGWBS scores were significantly lower in the patient group compared with reference population, both at baseline (median score 61.0 (IQR 46.0–83.0) vs 89.5 (IQR 81.0–95.7), $P < 0.001$) and follow-up (median score 61.0 (IQR 46.0–83.0) vs 89.5 (IQR 81.0–95.7), $P < 0.001$).

Baseline and follow-up PGWBS scores were not statistically different for the subgroup of 23 patients. Positive well-being, general health and vitality were the mostly under-marked domains.

Conclusion
Our results demonstrate impairment of QoL in acromegaly, which fails to improve despite long-term disease control. A more holistic approach, potentially in a multi-disciplinary setting involving clinical psychologists, should be implemented.

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**GP.19.04**

**Molecular and pathological determinants of somatostatin analogue resistance: somatotropinomas in AIP mutated and X-LAG syndrome patients**

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Poor hormonal and tumour responses to somatostatin analogues (SSA) in acromegaly can occur although the aetiology is often unclear. Two genetic syndromes are associated with relative SSA resistance: acromegaly due to AIP mutations (AIPmut) and the newly described X-linked acrogigantism (X-LAG) syndrome due to chromosome Xq26.3 microduplications. We studied whether SSA resistance in these conditions was related to somatostatin receptor (SSTR) levels in tumour tissues. We studied six XLAG and seven AIPmut patients, none of which had hormonal control on chronic SSA therapy, and ten mutation-negative patients (controls). Immunostains were evaluated semi-quantitatively and an immunoreactive score (IRS) was recorded for each section. Staining was assessed as negative for IRS 0–1, weakly positive for IRS 2–3, moderately positive for IRS 4–8, and strongly positive for IRS > 8. In AIPmut cases, one was negative for SSTR2, two for SSTR5 and three for SSTR1. SSTR3 was the most highly expressed receptor in both acromegaly controls (average IRS 9.8) and in AIPmut (average IRS 9.5) somatotropinomas. SSTR1 and SSTR5 were present at higher levels in the controls vs AIPmut cases. The difference between AIPmut and controls was statistically significant for SSTR1 ($P = 0.039$) but not for SSTR5 ($P = 0.239$). Interestingly, the expression level of SSTR2 was significantly higher in the control somatotropinomas (average IRS 7.9) compared with the AIPmut (average IRS 2.3) adenomas ($P = 0.0026$). Furthermore, in the AIPmut somatotropinomas, six out of seven samples had SSTR2 IRS scores < 3, while in controls only three out of 13 had SSTR2 IRS < 3. In XLAG syndrome cases, SSTR2 and SSTR3 were expressed in all samples analyzed, while one was negative for SSTR1, and another was negative for SSTR5. We observed that the expression of SSTR2 was variable but moderate to high in all cases (IRSs 4–10), despite the poor to absent SSA responses. SSTR3 was also highly expressed (average IRS 8.8) in the analyzed XLAG tumours, while the levels of SSTR1 and SSTR5 were lower than that of SSTR2 in these cases. Despite both having poor responses to SSA, variable expression of SSTR2 occurs in AIPmut and XLAG syndrome somatotropinomas. SSTR3 appears to be highly expressed in somatotropinomas, irrespective of the genetic background.

Disclosure
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**GP.19.05**

**Clinical and biochemical outcomes during pregnancy in patients with acromegaly**

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Acromegaly is a rare condition resulting from excess secretion of GH and IGF1. Acromegaly is frequently associated with subfertility. As such there is little data on the course of the disease during pregnancy, and of the effects of the disease and its treatments on the foetus.

Objective
We describe known pregnancies in women with acromegaly within the Republic of Ireland over a 15-year period.

Methods
We collected clinical, biochemical, and outcome data during and following pregnancy.

Results
We have identified 11 pregnancies in eight women. All women had a pituitary macroadenoma. In eight cases there was concurrent prolactin hypersecretion. Ten out of 11 patients were medically treated prior to conception. Dopamine agonists were most commonly used (8/11) followed by somatostatin analogues (4/11). One patient was treated with both dopamine agonists and somatostatin analogues. In 7/11 cases dopamine agonist therapy was continued throughout the pregnancy. Median IGF1 at conception was 240% above the upper limit of the age related reference range (IQR 230–380%). At the time of conception 2/11 cases had IGF1 levels within the age related reference range. During the third trimester IGF1 was within the reference range in 6/10 cases, and in all cases IGF1 levels fell during pregnancy. One patient was treated for hypertension throughout two pregnancies. No patient developed diabetes mellitus or any neurological complications during pregnancy. All babies were delivered via elective Caesarean section at term. Four babies were breastfed post delivery. Mean birth weight was 2.8 kg, with no cases of macros- or microsomia.

Conclusions
Our data suggests that pregnancy in acromegalic women is not associated with excess morbidity to mother or baby. There is a high rate of Caesarean section. Our data correlates with previous studies showing a beneficial effect of pregnancy on biochemical control of acromegaly.

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Criteria for disease control in acromegaly under SSA treatment: mean GH profile or GH random?
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Acromegaly is due to increased GH secretion usually sustained by a GH-secreting pituitary adenoma. Somatostatin analogues (SSA) can control GH hypersecretion in 60% of patients and tumor volume in 30%. The disease control is, in turn, associated with lower mortality and therefore to verify the optimal control of the disease activity is of critical importance to adapt the dose and the choice of alternative treatment. The criteria for optimized disease control had been assumed as mean GH <2.5 ng/ml and normal for age IGF1 levels. In 2010 a consensus proposed as new criteria GH random (GHR) <1 ng/ml and normal for age IGF1 levels. We compared the reliability of new mean GH profile (GHP) <2.5 and GHR <1 ng/dl as a good marker of disease activity in acromegaly; we also evaluated the association between GH levels (mean and random) and IGF1/IGFBP3 levels.

To this goal in an observational and retrospective study, we enrolled 34 responsive to SSA treatment acromegalic patients (25F, 33–86 years). The clinical response had been defined by normal IGF1 levels and no clinical activity. In all subjects the dose of SSA had been stable in last 2–5 years. In all subjects in phase 1 (before 2010) mean GHP, IGF1, and IGFBP3 and in phase 2 (after 2010) GHR, IGF1, and IGFBP3 had been evaluated. In all subjects in both phases of the study IGF1 (phase 1: 186.8 ± 10.0 and phase 2: 175.0 ± 37.3) and IGFBP3 (phase 1: 2.7 ± 0.1 and phase 2: 2.2 ± 0.1) levels were normal (20.0 ± 0.6) levels are higher (P = 0.1) than GHP (1.17 ± 0.57 ng/ml). Concordance between GHR <2.5 ng/ml and normal IGF1 was demonstrated in 85.3% of patients while between GHR <1 ng/ml and normal IGF1 just in 29.4% (P < 0.01). Our study shows that in acromegalic patients responsive to SSA, GHP <2.5 ng/ml but not GHR <1 correlate with normal IGF1 levels, thus indicating that evaluation by GHP would more reliably reflect an appropriate disease control.

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Patient experience of living with acromegaly in the UK
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61 patients (104 invited participants), within 10 years of active treatment for acromegaly, from five hospitals in the South West Peninsula (UK) (one neurosurgical centre) were interviewed to explore the experience of living with acromegaly, from five hospitals in the South West Peninsula (UK) (one neurosurgical centre) were interviewed to explore the experience of living with acromegaly, access to information, support and their ability to make decisions about their care. Semi-structured interviews by an independent consultant (60–120 min each) included 34 males and 27 females; 25–85 years old; 52 (85%) patients had surgery, 56 (92%) experienced a significant delay from symptoms to diagnosis, but prompt effective secondary care treatment. Communication and coordination of care between teams was criticised. Patients felt a lack of psychological and emotional support. Those in contact with a ‘specialist’ consultant or an endocrine nurse specialist felt most supported. 52 (85%) felt they had access to a consultant who understood the condition. Those without contact with an endocrine nurse specialist felt their care might have been compromised as a result. Patients felt unprepared for the life-long effect of their condition. 36 (59%) were on additional medical treatment and had issues with the ordering, dispensing or administering of the drug. 46 (75%) would be willing to travel anywhere in the UK to receive treatment (25% to next available hospital) if not available locally. Although, many felt involved in decision-making, few had been offered choice (but would value their consultant’s advice). Whilst 53 (87%) patients felt they understood about their condition now, many felt this took a long time with extensive personal research. 67% had been offered written information, 69% had looked on websites, 61% were aware of patient groups but only 20% had joined or sourced information from 1 and 15% attended a meeting (despite a desire to help others with acromegaly). This is the largest acromegaly qualitative patient experience study undertaken in the UK, reflecting the issues of living with acromegaly.

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Effects of long-term combined treatment with somatostatin analogues and pegvisomant on cardiac structure and performance in acromegaly
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Somatostatin analogues (SA) are known to revert acromegalic cardiomyopathy mainly in young patients with short disease duration, whereas pegvisomant (PEG) reportedly improves cardiac structure and performance in patients resistant to SA. To date, no data are available on the effects of long-term SA + PEG on cardiovascular complications. The current study aimed at investigating the effects of long-term SA + PEG on cardiac structure and performance in acromegaly. Thirty-six acromegalic patients (14M, 22F, aged 52.3 ± 10.2 years) entered the study. Weight, BMI, systolic (SBP) and diastolic (DBP) blood pressure, IGF1, fasting glucose (FG), fasting insulin (FI), HOMA-IR, HbA1c and lipids were evaluated at diagnosis (T0), after long-term (median 36 months, range 6–156 months) SA (T1) and after 12 (T12) and 60 (T60) months of SA + PEG, with last follow up (LPU) being performed after a median time of 78 months (range 60–144 months). At each time point all patients underwent echocardiography. SA induced a slight but not significant decrease in IGF1 (P = 0.077), whereas FI (P = 0.000), HOMA-IR (P = 0.013), ejection fraction (EF; P = 0.013), early (E) to late (A) ventricular filling velocities (E/A; P = 0.001) and isovolumetric relaxation time (IVRT, P = 0.001) significantly improved. At T12 weight (P = 0.004), BMI (P = 0.005), IGF1 (P = 0.001), HOMA-IR (P = 0.000), left ventricular mass index (LVMi, P = 0.000) and E/A (P = 0.006) significantly improved compared to T0, with HOMA-IR further improving (P = 0.000) compared to T1. At T60, IGF1 (P = 0.001), FI (P = 0.001), HOMA-IR (P = 0.000), left ventricular mass index (LVMi, P = 0.000), E/A (P = 0.05) and IVRT (P = 0.014) significantly ameliorated compared to T0. At LFU IGF1 normalized in 83.3%; IGF1 (P = 0.043), FI (P = 0.000), HOMA-IR (P = 0.000), HDL (P = 0.031), EF (P = 0.035), LVMi (P = 0.000), E/A (P = 0.02) and IVRT (P = 0.001) significantly improved compared to T0. PEG dose significantly correlated with LVMi at T12 (r = 0.575, P = 0.000) and T0 (r = 0.403, P = 0.037). In conclusion, long-term PEG addition to SA improves cardiac structure and performance, particularly diastolic dysfunction, in acromegalic patients resistant to SA.

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Management of pasireotide-induced hyperglycaemia with proactive monitoring and early intervention: key learnings from the phase III, 24-week PAOLA study
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Introduction
In PAOLA study, pasireotide showed superior efficacy over continued treatment with octreotide/lanreotide in patients with inadequately-controlled acromegaly: 64% of patients receiving pasireotide long-acting release (LAR) reported hyperglycaemia-related adverse events. Pasireotide has been shown to inhibit insulin secretion. The aim of this exploratory analysis was to investigate the effect of timing of antidiabetic medication (ADM) intervention on the fasting plasma glucose (FPG) outcome during pasireotide LAR treatment.

Methods
Patients randomised to pasireotide LAR, who received ≥ 1 dose of pasireotide and had a valid post-baseline safety assessment (safety population for pasireotide; n = 125), were included and categorised by baseline diabetic status: non-diabetic; pre-diabetic (FPG 100–< 126 mg/dl or HbA1c 5.7–< 6.5% or 2 h post-OGTT glucose 140–< 200 mg/dl); diabetic (current/prior ADM use or FPG ≥ 126 mg/dl or HbA1c ≥ 6.5% or 2 h post-OGTT glucose ≥ 200 mg/dl).

GP 19.06

GP 19.07

GP 19.08

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Results
Hyperglycaemia (first occurrence of FPG ≥ 126 mg/dl or HbA1c ≥ 6.5% in non-diabetic/pre-diabetic; or first occurrence of FPG or HbA1c increase ≥ 20% from baseline in diabetic) was experienced by 5/19 non-diabetic, 9/24 pre-diabetic and 68/82 diabetic patients. Due to fewer non-diabetic/pre-diabetic patients, the analysis is focused on 68 diabetic patients. ADM was initiated/adjusted in 36/68 diabetic patients after 0–2 weeks (mean ± SD: 7.4 ± 2.7 weeks; median duration: 6.5 weeks) of pasireotide treatment. A significant (P < 0.05) FPG change ≥ ±10 mg/dl at week 2 (maximum follow-up) was -110.9 ± 96.3 mg/dl (from 255.9 ± 89.8 mg/dl during occurrence of hyperglycaemia). -7.3 ± 91.1 (from 186.9 ± 92.2) and 2.1 ± 78.9 (from 178.7 ± 38.0), respectively. Mean FPG change was -10.7 ± 91.5 mg/dl (from 152.4 ± 44.0) in patients who did not receive ADM (n = 32). Significant (P < 0.01) factors predicting hyperglycaemia were BMI ≥ 25 kg/m2 (OR = 2.3), per unit increase in HbA1c (OR = 4.3) and diabetes at baseline (OR = 4.8); and history of dyslipidaemia (OR = 3.6).

Conclusions
Pasireotide-induced hyperglycaemia can be managed with proactive monitoring and early intervention (e.g., within 2 week if FPG > 250 mg/dl). These data suggest that in patients receiving pasireotide, early intervention can improve hyperglycaemia control.

Disclosure
This work was supported by Novartis.

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GP.19.10

A phase 2 study of antisense oligonucleotide therapy directed at the GH receptor demonstrates lowering of serum IGF1 in patients with acromegaly.

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ATL1103 is a second generation antisense oligomer directed at the GH receptor. It is a 20mer with a phosphorothioate backbone and 2′-O-methoxyethyl modifications of the five nucleotides at either end intended to increase its plasma degradation. We report a phase 2 randomised, open-label, parallel group study of subcutaneously administered ATL1103 in patients with active acromegaly. Appropriate ethical approval was obtained in each centre and the study is registered as EudraCT 01203014730. Patients gave written informed consent. The protocol entailed appropriate washout from ongoing medical therapy after which IGF1 had to be at least 1.3 times age-related ULN. Patients were randomised to receive either ATL1103 200 mg once or twice weekly for 13 weeks. After completion of drug administration, patients were monitored for a further 8 weeks. The primary objectives were to evaluate the safety and pharmacokinetics, 34 patients were recruited in 13 centres and 26 (mean age 50.4 years; 11 male) were randomised, and all completed treatment. ATL1103 was well tolerated with mild to moderate injection site reactions being the most common drug-related AE. Four SAEs were reported (three in a single patient) but none were felt to be study drug related. Two patients withdrew at completion of dosing. There was a significant fall in serum IGF1 of 26% by week 14 with 200 mg twice weekly (377 ± 198 vs 411 ± 174 mg/ml (mean ± s.d.), P < 0.0001) although the nadir had not been reached. Once weekly dosing did not result in a significant fall in IGF1. The fall in IGF1 with twice weekly dosing was associated with a mean reduction ring size circumference of 1.15 mm (P = 0.014) and an increase in GH (P = 0.003). This study provides proof-of-concept that ATL1103 is able to significantly lower IGF1 in patients with acromegaly.

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Pituitary - Hypopituitarism

GP.20.01

Reduced mortality due to malignant neoplasms in patients receiving long-term GH replacement therapy – a Swedish study based on more than 4000 patient-years

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Patients with hypopituitarism and untreated growth hormone (GH) deficiency have excess mortality. GH replacement therapy (GHRT) has many beneficial effects, but its impact on mortality has not been proven and there are still safety concerns regarding the potential cancer risk. We have therefore studied the mortality in non-functioning pituitary adenoma (NFPA) patients with and without GHRT. Only patients with NFPA were studied in order to eliminate the influence of the aetiology of hypopituitarism.

NFPA patients within the Sahlgrenska University Hospital’s catchment-area (1.5 million inhabitants) were identified through the Swedish National Patient Registry. The records of all identified patients were reviewed. All patients were cross-referenced with the Swedish National Death Registry. The study period was 1987–2011. Standardised mortality ratios (SMRs) with 95% CIs (reference: Swedish population) were calculated.

We identified 455 patients with NFPA, out of which 433 had complete records and were included in the study. GHRT had been used for at least one year by 187 patients and 246 patients had not been treated with GHRT. Mean (± s.d.) age at diagnosis was lower (P < 0.001) in the GHRT-group (54.3 ± 11.7) than in the non-GHRT-group (64.0 ± 15.4). Mean duration of GHRT was 10.9 (6.1) years and mean follow-up time in the non-GHRT-group was 6.9 (5.4) years. The total number of deaths in the study was 83. The overall SMR was 0.49 (0.27–0.80, P = 0.003) for the GHRT-group and 0.98 (0.76–1.24, P = 0.94) for the non-GHRT-group. The SMR was significantly lower in the GHRT-group compared to the non-GHRT-group (P = 0.02). SMR for malignant neoplasms was significantly reduced in the GHRT-group (0.19; 0.02–0.68; P = 0.003), and was not significantly changed in the non-GHRT-group (0.74; 0.37–1.31; P = 0.37).

This is the first study to report a reduced mortality in NFPA patients receiving long-term GHRT. Furthermore, mortality due to malignant neoplasms was decreased in the GHRT-group and not in the non-GHRT-group.

Disclosure
This study received financial support from the Swedish government under the ALF-agreement.

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GP.20.02

Association of serum IGF1 concentration with cardiovascular function in adults with GH deficiency with different GH treatment regimes: a randomised clinical trial

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Objective
Epidemiological evidence for a link between serum IGF1 concentration and cardiovascular disease in the general population and in patients with GH deficiency or hypersecretion has been demonstrated. However, the underlying mechanisms remain unresolved. We investigated associations between IGF1 levels within the reference range and different measures of cardiovascular function and risk factors in substituted GH deficient adults within a randomised clinical trial.

Methods
Thirty-two subjects receiving GH therapy for at least a year with a stable IGF1 concentration of -1 to 1 SDS were included and randomised to receive either a decrease of their regular dose (IGF1 target level: -2 to -1 SDS) or an increase of their dose (IGF1 target level: 1 to 2 SDS) for a period of 6 months. Measurements of micro- and macrovascular function, lipid profile, inflammation, and insulin resistance (HOMA-IR) were performed.

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GP 20.03
Timing is everything? Postpartum pituitary dysfunction – variability of clinical and radiological presentation
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Introduction
Two aetiologies are responsible for postpartum hypopituitarism: Sheehan’s syndrome which develops following traumatic labour, and lymphocytic hypophysitis. Since management of lymphocytic hypophysitis does not require surgery in most cases, pathology is usually absent, and the clinical presentation, in combination with laboratory and imaging characteristics establish the diagnosis. We aimed to describe the various patterns of presentation, including assisting analyses, among women with probable lymphocytic hypophysitis.

Methods
A retrospective study of women with pituitary dysfunction presented immediately or several months following delivery. Clinical characteristics data, pituitary hormone levels, and imaging findings were collected.

Results
Eight women were included; mean age at delivery was 34.8 ± 7.4 years. Most patients (68%) presented with breastfeeding difficulty, and 5/8 reported headache. Among the patients with headache, 2/5 presented during pregnancy, and the others – 2, 4 and 9 months following delivery. Hypopituitarism symptoms appeared immediately after delivery in half of the patients, between 7–12 months in 3/8; in one patient severe headache was the sole complaint. All patients had central hypocortisolism, hypogonadotrophic hypogonadism, and growth hormone deficiency, and 7/8 had central hypothyroidism. Prolactin levels were low in 2/8.

Conclusions
IGF1 level within the reference range in GH treated adults is related to microvascular endothelial activity, inflammation, and metabolic insulin resistance.

Disclosure
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GP 20.04
Irradiation-induced hypopituitarism in adult brain tumour survivors: single-centre longitudinal data
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Introduction
Radiation-induced hypopituitarism is a well-recognized complication of cranial radiotherapy (cXRT) for childhood brain tumours when the hypothalamo-pituitary axis is within the irradiation field. Few data are available for survivors of adult brain tumours who have received cranial irradiation.

Methods
We retrospectively reviewed medical records of patients referred to Endocrinology following cXRT for primary non-pituitary brain tumours during adulthood. Longitudinal data regarding pituitary-related treatment outcomes were collected. The ITT and/or GST were used to assess GH and HPA axes integrity. Basal values for the additional anterior pituitary hormones were used to determine gonadotropin, TSH and prolactin status.

Results
107 patients (mean age 40.0 ± 13.1 years) with mean duration of post-cXRT follow-up of 9.1 ± 5.7 years were studied. 32.7, 19.6, 20.6 and 27.1% of patients had tumours located in the anterior, middle, posterior cranial fossa and central (perisellar) regions respectively. 94.4% received fractionated photon radiotherapy (mean dose 51.7 ± 6.5Gy, mean number of fractions 28.6 ± 3.5), while the remaining patients received proton beam or stereotactic radiotherapy. Evidence of pituitary dysfunction was present in 88.8% of patients. The GH axis was affected in 86.9% of patients (severe GHD 64.5%, partial GHD 22.4%), followed by LH/FSH (34.6%), ACTH (23.4%), and TSH (11.2%) axes. Clinically significant ACTH deficiency necessitating glucocorticoid replacement was present in only 10.3% of cases. Hyperprolactinaemia was noted in 15.0% of patients. Single pituitary axis dysfunction was found in 41.1% of patients, while multiple axes were affected in 47.7% of cases. Longitudinal data analysis showed accumulation of pituitary hormone deficits the longer the duration of follow-up.

Conclusions
Pituitary dysfunction in survivors of adult brain tumours following cXRT is very common. The majority of deficits develop within 5 years post-cXRT, however late onset or progression of severity of a previously developed hormone deficiency was also observed. Long-term follow-up of these patients in specialist endocrine centres is strongly recommended.

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GP 20.05
Long-term follow-up of 520 patients with non-functioning pituitary adenomas from two large tertiary referral centres: a UK-Republic of Ireland collaborative study
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Abstract
Non-functioning pituitary adenomas (NFPA) are the most common pituitary tumours, often presenting with chiasmal compression or hypopituitarism. Surgical resection, accompanied by radiotherapy (RTX) in selected cases, is the treatment of choice for compressive tumours. Long-term health consequences of NFPA and their treatment are unclear. In this retrospective study, we aimed to assess long-term pituitary function, recurrence and mortality in a large NFPA cohort across two tertiary centres. Case-note review of all patients treated for NFPA in Queen Elizabeth Hospital Birmingham and Beaumont Hospital Dublin between 1997 and 2012 was performed; data on patients treated before 1997 was included where available. Clinical presentation, imaging characteristics, long-term pituitary function and co-morbidities were recorded in each case. Data on mortality was recorded via Clinical Portal in Birmingham and from GP contact in Dublin.

519 patients were included in the analysis (Birmingham n = 271; Beaumont n = 248; 59.2% male, mean age at presentation 55.2 ± 14.1 years). Mean duration of follow-up was 8.5 ± 6.3 years (0.5–43). 90.8% of patients underwent surgery (81.1% transphenoidal). 184 patients (35.4%) underwent pituitary radiotherapy, either postoperatively (43.5%) or at recurrence.
Background and objective

Atypical pituitary adenomas (APA), in 2004, were defined according to WHO classification, as those with Ki-67 > 3%, excessive p53 expression and increased mitotic activity and invasive behaviour. The real usefulness of this classification is still controversial, so we reviewed compared clinical and prognostic features in our typical and atypical pituitary adenomas.

Patients and methods

We retrospectively reviewed 343 consecutive pituitary adenomas (PAs). APAs occurred in 18.7% of cases. All patients were operated on in the Department of Neurosurgery at our institution and followed up at the Hypothalamic-Pituitary Disease Unit of the same institution. None patient had an adjuvant treatment pre-neurosurgery. Median follow-up time in our series was 75 months (range: 7-345 months).

Results

More frequently APAs were diagnosed in younger patient. However we found a similar prevalence of APAs in male and female patients. A higher risk of being affected for an APA was identified in cases characterised by an ACTH- and PRL-immunohistochemical positivity. According to WHO classification, cavernous sinus invasion was associated with higher risk of being affected of an APA and consequently a higher risk of a partial PA neurosurgery resection. In our series we separately analysed recurrence and disease free survival time (DFST) in patients undergone radical neurosurgery (219 cases). In this group of radically resected PAs, we find a similar risk of recurrence-disease and a superimposable DFST between typical and atypical pituitary adenomas. Moreover, in this series we found that Ki-67 expression > 1.5% was associated to a higher risk of recurrence and to a worse DFST, even after correction for age at diagnosis, gender, immunohistochemical classification, tumor size, invasiveness and Knoss classification (P = 0.01; HR: 2.572; 95% CI: 1.251–5.285). PAs with Ki-67 ≤ 1.5% showed a worse DFST as compared to PAs with Ki-67 > 1.5% (HR: 2.166; 95% CI: 1.154–4.064).

Conclusion

In this series, atypical and typical PAs didn’t differ for recurrence and DFST. PAs with Ki-67 > 1.5% showed a higher recurrence risk and a worse DFST as compared to PAs with Ki-67 < 1.5%. We suggest that a Ki-67 > 1.5% may be useful as prognostic marker.

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Guidelines, cabergoline was reduced to 250 mcg twice-weekly. 24-months later serum prolactin remained well-controlled (76 mU/L), and substantial (>50%) tumour shrinkage was evident on MRI.

Conclusions
These cases demonstrate that a delayed radiological response may be seen without further dose escalation, once biochemical normalisation has been achieved in prolactinomas; current guidelines may therefore inappropriately categorise such tumours as ‘dopamine agonist resistant’. Our literature and local database review suggests this may be an under-recognised phenomenon. Furthermore, the case described here highlights the utility of functional imaging in aiding management in such patients.

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GP 20.09
Thyrotropinoma: diagnosis and management of a rare but increasingly recognised pituitary tumour – novel insights from a large prospective UK study
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Background
Thyrotropinomas (TSHomas) are traditionally considered a rare, albeit important cause of thyrotoxicosis. Although early case series reported a predominance of invasive microadenomas, emerging evidence suggests microadenomas are being increasingly diagnosed, and the clinical/biochemical phenotype appears to be more variable than previously suspected. We therefore performed detailed phenotyping of patients referred to our centre with a diagnosis of TSHoma over a 4-year period.

Methods
35 patients with hyperthyroxinaemia and non-suppressed TSH were studied prospectively. Laboratory assay artefact, confounding intercurrent illness/drug therapy and TRH/THRB mutations were excluded in all cases. Further investigations included: hyperthyroid symptom score, measurement of resting energy expenditure, sleeping heart rate, bone mineral density, sex-hormone-binding globalina (SHBG), alpha-subunit (ASU); TSH molar ratio, TRH test, OGTT, octreotide (100 mcg) suppression test (OST), volumetric MRI (vMRI) and 11C-methionine PET-CT. Patients then proceeded to a formal trial of depot somatostatin analogue (SSA) therapy.

Results
Clinical/metabolic features varied markedly, ranging from euthyroid to overtly hyperthyroid, and were not clearly correlated with the degree of hyperthyroxinaemia. Similarly, SHBG and ASU:TSH did not reliably identify many cases (both raised in <50%), especially microadenomas. In contrast, a blunted TSH response to TRH (<4.5-fold rise), combined with normalization of thyroid function during a 3 month trial of SSA therapy, was observed in 90% of cases. Interestingly, TSH and FT3 responses in the OST did not predict efficacy of depot SSA, 50% of patients had microadenomas, with several not reliably visualised using conventional MRI. In these patients, vMRI combined with PET/CT identified the site of the microadenoma. All 35 patients received SSA as a bridge to surgery or vMRI and functional imaging may be helpful in informing the surgical approach.

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Pituitary - Diagnosis of Cushing’s disease
GP 21.01
A reappraisal of second line tests in the differential diagnosis of ACTH-dependent Cushing’s syndrome: the role of three dynamic tests
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Introduction
The diagnosis of Cushing’s syndrome (CS) might be challenging especially in ACTH-dependent CS when it comes to detect the origin of ACTH secretion.

Materials and methods
We retrospectively recorded data about 170 patients with ACTH-dependent CS (149 CD, 21 EAS) referring to two Endocrinology Units. We focused especially on the performance of 3 dynamic tests: the dexamethasone 8 mg overnight challenging (HDDST), the CRH and the desmopressin (DDAVP) test.

Results
Patients with EAS were slightly older and had higher 0800 h. ACTH levels, 0800 h. and 1 mg dexamethasone cortisol levels, and FT4 than patients with CD (P < 0.01). On the contrary, CD patients had a greater ACTH and cortisol response after CRH injection (P < 0.0001) and also a more pronounced decreased of cortisol after HDDST (P < 0.0001). A threshold for ACTH increase after CRH stimulation of 72% was able to identify CD with a sensitivity (SE) of 95% (95% CI: 68–83%) and a specificity (SP) of 82% (95% CI: 83–100%). Regarding HDDST, a cortisol reduction >53% suggested a pituitary origin with SE of 88% (95% CI: 81–93%) and SP of 90% (95% CI: 68–99%); the latter could be increased to 100% by moving the cut-off to 75% of decrease. The AUC of CRH test and HDDST was 0.93 (95% CI: 0.89–0.97) in both cases (P = ns). There were no EAS with both positive responses to these 2 tests. ACTH and cortisol increases after DDAVP test were also higher in CD than in EAS (P < 0.01), but they added very little to the power of the other dynamic tests.

Patients with CD showed an increased response to both HDDST and CRH; the cut-offs found had good SE and SP in discriminating patients from CD with those from EAS. Lack of response of both tests was highly suggesting of EAS. On the contrary when both tests gave positive responses it indicated CD. We also confirmed the limited role of DDAVP test in this diagnostic phase. In conclusion, dynamic tests may play an important tool in the differential diagnosis of ACTH-dependent CS.

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GP 21.02
Bilateral inferior petrosal sinus sampling reliably differentiates pituitary from ectopic Cushing’s, but frequently fails to predict pituitary tumour location, especially when lateralizing to the right
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Background
BIPSS remains the gold standard for differentiating pituitary and ectopic sources in ACTH-dependent Cushing’s syndrome. A pituitary:peripheral ACTH ratio > 2 in the basal state, and/or >3 following CRH stimulation, is considered indicative of pituitary Cushing’s, with a range of sensitivities and specificities cited in the literature. In addition, in Cushing’s disease a peak interpetrosal gradient of >1.4 has been reported to predict the site of the adenoma in approximately 2/3 of cases. We examined the performance of BIPSS against these criteria in a cohort of patients who had undergone the procedure in our centre over the last decade.

Methods
39 patients with biochemically proven ACTH-dependent Cushing’s, who had undergone BIPSS and had either subsequent histological confirmation of the ACTH source, or significant improvement/cure of their Cushing’s following transphenoidal surgery, were included in the study.

Results
Based on basal ACTH levels (pre-CRH stimulation), 89% of patients were deemed to have pituitary Cushing’s and 11% an ectopic source. Post-CRH stimulation 94% of patients reached the cut-off for pituitary Cushing’s. This gave a sensitivity of 97% and a specificity of 100% for pre-CRH stimulation and 100% sensitivity and 67% specificity for post-CRH stimulation. Two thirds (65%) of BIPSS procedures exhibited lateralisation to the right side, but this was subsequently shown at surgery to be correct in only half of the patients. In contrast, left lateralisation had a much higher positive predictive value (80%). When combined, lateralisation (either right or left) was accurate in only 60% of cases.

Conclusions
Predominance of right sided lateralisation on BIPSS may signify a ‘dominant’ right sinus in many patients undergoing this procedure. We suggest therefore that whole gland exploration is particularly important in ‘right sided’ BIPSS cases, and additional pituitary imaging (e.g. volumetric MRI, functional imaging) may be helpful in informing the surgical approach.

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**GP.21.03**

**Altered neural processing during emotional faces in remitted Cushing’s disease**

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**Background**

Patients with long-term remission of Cushing’s disease (CD) demonstrate residual psychological complaints. At present, it is not known how previous exposure to hypercortisolism affects psychological functioning in the long-term. In foregoing Magnetic Resonance Imaging (MRI) studies, abnormalities of brain structure and resting-state connectivity were demonstrated in patients with long-term remission of CD. However, no data are available on functional alterations in the brain during the performance of emotional or cognitive tasks in these patients.

**Objective**

To investigate brain activation during emotion processing in patients with long-term remission of CD.

**Design**

A cross-sectional functional MRI study.

**Methods**

Processing of emotional faces versus a non-emotional control condition was examined in 21 patients with long-term remission of CD and 21 matched healthy controls. Functional MRI analyses focused on activation and connectivity of two a priori determined regions of interest: the amygdala and the medial prefrontal cortex (mPFC). In addition, we assessed psychological and cognitive functioning, and clinical disease severity.

**Results**

Patients with long-term remission of CD showed hypoactivation in the mPFC during processing of emotional faces in patients relative to controls. In addition, functional coupling between the mPFC and posterior cingulate cortex (PCC) was decreased. No differences were found in the activation of the amygdala.

**Conclusion**

The present study is the first to show alterations in brain function and functional coupling in patients with long-term remission of CD relative to matched healthy controls. These alterations in brain function may, together with abnormalities in brain structure, explain the persisting psychological morbidity these patients after long-term remission.

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**GP.21.04**

**Exaggerated and additive ACTH responses following the combined ghrelin + CRH test in patients with Cushing’s disease**

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Ghrelin is able to stimulate HPA axis in both humans and animals. Exaggerated ACTH and cortisol responses to ghrelin have been shown in patients with CD. Here we studied the role of ghrelin alone or in combination with CRH in the diagnosis of CD. In 21 CD patient (18 female, age 49.8±10.2 years, BMI 29.8±0.8 kg/m2; ten macroadenomas 11 microadenomas) we performed: i) ghrelin test (100 μg iv bolus) ii) CRH test (100 μg iv bolus) and iii) ghrelin + CRH in random order, one week apart. We also included 8 (seven female, age 40.6±5.3 years, BMI 29.9±1.2 kg/m2) control subjects (C) in the study. Peak ACTH, cortisol, PRL and GH responses to ghrelin and/or CRH were evaluated (mean ± s.e.). At baseline, ACTH (CD: 71.2±15.6 ng/l; C: 18.9±4.1 ng/l; P<0.01) and cortisol levels (CD: 643.1±41.7 nmol/l; C: 316.4±23.7 nmol/l P<0.01) were significantly higher in CD vs C. After ghrelin administration peak ACTH (CD: 192.3±40.4 ng/l vs C: 71±30.9 ng/l, P<0.01) and cortisol responses (CD: 979.8±46.5 nmol/l vs C: 529.3±74.8 P<0.01) were significantly higher in CD compared with C but similar with ACTH (CD: 179±26.5 ng/l vs C: 59.8±12.3 ng/l, P<0.01) and cortisol responses (CD: 1088.7±51.4 nmol/l vs C: 677.3±71.3 nmol/l, P<0.01) to CRH in both patients with CD and controls. Following the co-administration of ghrelin + CRH an additive ACTH response was observed in both groups (CD: 384.1±74.2 ng/l; C: 176.3±48.5 ng/l) but at a different level. ACTH and cortisol responses, during all three tests, were similar in CD patients with micro- and those with macroadenomas. After stimulation with ghrelin the peak. PRL responses (CD: 1046.6±179.7 mU/l; C: 998.4±222.4 mU/l; P>0.05) were similar in CD compared to C, while GH responses (CD: 21.2±3.7 mU/l; C: 54.6±9.1 mU/l; P<0.05) were significantly lower in CD. Our results show that ACTH and cortisol secretion remain regulated and responsive to trophic stimuli in patients with CD, which are characterised by exaggerated ACTH and cortisol responses to ghrelin. Additive ACTH responses to the combined ghrelin + CRH administration, suggest that their ACTH releasing activities may be mediated independently in both patients and controls.

**Disclosure**

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**Diagnosis**

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**GP.21.05**

**Mental fatigue and executive dysfunction in patients with Cushing’s syndrome in remission**

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**Background**

Patients with Cushing’s syndrome (CS) in remission often suffer from impaired quality of life and cognitive dysfunction. Mental fatigue is characterized by mental exhaustion which appears especially during sensory stimulation or following mentally strenuous tasks. Other typical features are long recovery time for restoration of mental energy, irritability, impaired memory and concentration and sensitivity to stress, light and noise. The primary aim of this study was to investigate the occurrence of mental fatigue by using the recently developed mental fatigue scale (MFS) in patients with CS in remission. The secondary aim was to examine whether the more demanding parts C and D of the trail making test (TMT) are more sensitive, compared to the conventional parts A and B, to evaluate speed proceeding, visual search, motor performance and executive functioning.

**Methods**

This was a cross-sectional study including 51 patients with CS in remission and 51 controls, matched by age, gender and education. All subjects completed the self-administered MFS and performed all four parts of the TMT.

**Results**

The mean (± s.d.) age of patients and controls was 52.5±14.6 years and 53.6±13.9 years (P=0.7), respectively. The median time in remission was 12 (4–18) years. The patients had higher scores on all components of the MFS, indicating worse outcome, except for sensitivity to noise. The mean total score on the MFS was 13.5±7.4 in the patients compared to 7.8±4.9 (P<0.001) in controls. After adjustment for fatigue, depression and anxiety the patients performed worse on part D of the TMT (P<0.05) but not on parts A, B and C.

**Conclusions**

Mental fatigue is common in patients with CS in remission. The most demanding part of the TMT, part D, is more useful to capture cognitive deficits in patients with CS in remission compared to the conventional parts A and B.

**Disclosure**

This project received financial support from the Swedish federal government under the LUA/ALF agreement and The Health and Medical Care Committee of the Regional Executive Board, Region Vastra Gotaland.

**Diagnosis**

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**GP.21.06**

**Prolactine and urinary free cortisol measurement improve inferior petrosal sinus sampling results in ACTH dependent Cushing’s Syndrome**

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**Introduction**

Inferior petrosal sinus sampling (IPSS) is considered to be the gold standard for confirming the source of ACTH secretion in patients with Cushing’s syndrome (CS). Prolactin measurement during IPSS can improve diagnostic accuracy and reduces false negative responses.

**Patients and methods**

56 patients with ACTH-dependent CS were included (45 F/11 M, mean age 43.6 ± 10.8 years and 90.1% Cushing’s disease) diagnosed since 2000. IPSS was performed in 27 cases (15 with PRL measurement, two excluded due to incomplete data). Depending on IPSS results were classified as typical IPSS response if basal ACTH ratio Central/peripheral (C/P) was > 2 and/or after CRH > 3, considering others as atypical. Response to surgical treatment and utility of PRL determination were analyzed.

**Results**

Cortisol response to high DXM suppression test was > 50% in 62.9%, and > 90% in 37% in Cushing’s disease. Preoperative pituitary MRI did not identify adenoma in 12.5%. MRI adenoma lateralization was concordant with surgical adenoma lateralization in 92.7%. IBR was typical in 46.3% (6/13) and there were significant differences typical vs atypical (basal ACTH C/P ratio, ACTH C/P ratio after CRH, peak time, urinary free cortisol (UFC) and PRL correction). Basal PRL ratio C/P was < 1.8 in all atypical IPSS and 50% of typical IPSS. Venograms were reviewed and ACTH C/P peak corrected with PRL was > 0.8 in Cushing’s disease, being most of them > 1.2 (5/7). Only two patients have an intermediate value (a cyclic Cushing’s disease 1.09 and a microadenoma 1.05). Four patients with atypical IPSS corrected with PRL, were referred to surgery and they meet remission criteria up today. After transsphenoidal surgery 90.9% of patients met remission criteria (100% of microadenomas and in those without previous MRI image).

**Conclusion**

PRL measurement in atypical IPSS allows reclassification, whereas in typical cases can be useful to validate the peak ACTH C/P. PRL elevation after CRH and its use in the correction of the ACTH C/P ratio does not interfere with the interpretation of ACTH C/P peak. It is essential to evaluate UFC to complete the assessment.

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**GP.22.02**

**Surgical outcome and factors associated with Cushing’s disease recurrence in 101 consecutive patients operated on by a single pituitary neurosurgeon: the Cleveland Clinic experience**

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**Background**

Transsphenoidal tumour resection (TSS) is the first-line treatment for Cushing’s disease (CD). With an experienced neurosurgeon, immediate remission rates > 80% are expected for patients with microadenomas (< 10 mm).

**Aim**

To report initial and long-term remission rates in a specialist centre, and to ascertain factors associated with disease recurrence after TSS.

**Methods**

Patients with CD (n = 101, 28M, 73F) having TSS by one neurosurgeon (RJW) at Cleveland Clinic between 2004 and 2013, with a minimum one-year follow-up. Glucocorticoids were withheld during and immediately after surgery; ACTH and cortisol were closely monitored postoperatively with a standard protocol to determine initial remission. After discontinuing hydrocortisone for surgically-induced adrenal insufficiency, long-term remission was defined by 24 h UFC > ULN, and/or late night salivary cortisol > ULN, and/or 8 AM serum cortisol > 1.8 mcg/dl after 1 mg overnight dexamethasone.

**Results**

Median (range) for age and follow up were 46 (15–87) and 4.33 (1–9.8) years, respectively. 74 patients had microadenoma, 27 macroadenoma. Initial remission rates were: microadenoma 89% (66/74), macroadenoma 63% (17/27). Initial non-remission occurred in 18 patients, ten macro- and eight microadenoma. Six of the 83 patients with initial remission have had recurrence of hypercortisolism requiring either repeat TSS or adjunctive therapy. At last follow-up, continuing remission rates are: microadenoma 90%, macroadenoma 74%; 14 (seven macro, seven micro) have persistent hypercortisolism. Macroadenoma (P = 0.003) and tumour invasion beyond the pituitary (P < 0.001) were associated with failure of initial remission and greater likelihood of late recurrence. Absence of tumour on pre-operative imaging was not associated with failure of initial remission.

**Conclusions**

Surgery by a dedicated neurosurgeon in a specialised pituitary centre gives excellent initial and long-term results for CD. Presence of adenoma extension beyond the pituitary and immediate post-operative ACTH and cortisol levels are highly predictive of long-term outcome.

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**GP.22.03**  
Impact of preoperative magnetic resonance in surgical care of patients with Cushing's disease  
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**Introduction**  
Cushing’s disease (CD) is a rare disorder caused by an ACTH-secreting pituitary adenoma. Transphenoidal surgery (TSS) is the recommended first-line treatment. However, an equivocal or even normal preoperative MRI can preclude the surgical management and the outcome of these patients.

**Objectives**  
Evaluate the relationship between preoperative MRI and TSS efficacy in patients with CD.

**Methods**  
Retrospective cohort study of patients with CD followed in our centre between 1977 and 2013 (n = 84). Patients who lost follow-up or with insufficient data on their personal records were excluded (n = 51). Statistical analysis: SPSS (21).

**Results**  
Thirty three patients, 29 (87.9%) women, with a median of 33 years (24–70) were included. All patients underwent TSS as first treatment option and were followed postoperatively during a median period of 8 years (1–28). Patients were divided in: Group A (n = 19), cured patients; and Group B (n = 14), patients with persistent (n = 5) or recurrent (n = 11) CD within a median of 12 months. No significant demographic and clinical differences were recorded between the two groups. Group B patients presented a greater frequency of non-diagnostic preoperative images (28.6% vs 10.5%). And, in patients with a precisely visualized pituitary lesion (n = 27), those of Group A presented significant lower tumour diameters (8.4 vs 13.9 mm, P < 0.01), a greater number of pituitary microadenoma (68.4% vs 35.7%, P < 0.05), and none invasive macroadenoma (0% vs 21.4%) compared to Group B patients. All patients with non-diagnostic preoperative MRI (n = 6) performed inferior petrosal sinus sampling (IPSS), with identification of lateralization of ACTH secretion in all patients (2/2) of Group A and one patient (1/4) of Group B. A pituitary adenoma (confirmed by pathological examination) was found in 84.2% patients of Group A but only in 50% of Group B.

**Conclusions**  
Precise preoperative localisation of a corticotroph adenoma, particularly a microadenoma, in preoperative MRI was associated with a greater efficacy of TSS and a higher probability of cure. Performance of IPSS can be useful in patients with non-diagnostic preoperative MRI.

**Disclosure**  
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**GP.22.04**  
Long-term (5 years) treatment of Cushing’s disease with pasireotide  
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**Background**  
In a large 12-month Phase III study, pasireotide led to rapid and sustained decreases in UFC and provided clinical benefit in patients with Cushing’s disease. Here, we report data following an open-label, open-ended extension.

**Methods**  
162 patients with persistent/recurrent or de novo Cushing’s disease were randomized in the core study. 58 patients with mean UFC ≤ ULN or clinical benefit at month 12 entered the extension. Dose titration was permitted at the investigators’ discretion (300–1200 μg s.c. bid). Efficacy data are presented for those patients who attended the visit at month 60; safety data are presented up to study end for all randomized patients.

**Results**  
16 and seven patients were ongoing at months 60 and 72, respectively; maximum exposure was 76.6 months. For patients who reached month 60, percentage change in median UFC (range) from core baseline was −82.6% (−96.5% to 324.0%; n = 16) and −81.8% (−94.9% to 3.4%; n = 15) at months 12 and 60, respectively; of these patients, 10/16 and 11/16 had UFC ≤ ULN at months 12 and 60, respectively. Percentage change in median ACTH (range) was −34.7% (−72.0% to 66.7%; n = 16) at month 12 and −8.3% (−68.0% to 100.0%; n = 16) at month 60. Improvements in clinical signs, including systolic and diastolic blood pressure, weight, BMI, and total cholesterol level, were observed by month 6 and were sustained up to month 60. The most common AEs reported from core baseline until study end were diarrhoea (58.6%), nausea (53.7%), hyperglycaemia (41.4%), and cholelithiasis (32.7%); diabetes mellitus was reported in 22.2% of patients.

**Conclusions**  
Initial reductions in UFC and improvements in clinical signs were maintained over 5 years of pasireotide treatment. No new safety signals were reported during long-term treatment. Results from this study suggest that pasireotide may be effective in the long-term treatment of Cushing’s disease.

**Disclosure**  
This work was supported by Novartis.

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**GP.22.05**  
Effects of osilodrostat (LCI699) on cytochrome P450 enzymes in healthy volunteers indicates a low drug–drug interaction potential  
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**Introduction**  
In vitro assessments of osilodrostat (LCI699), a potent oral inhibitor of 11β-hydroxylase suggested potential drug–drug interactions (DDIs) with cytochrome P450 (CYP) enzyme metabolism. This clinical study evaluated the effect of osilodrostat on the pharmacokinetics (PK) of CYP1A2, CYP2C19, CYP2D6, and CYP3A4 probe substrates, caffeine, omeprazole, dextromethorphan, and midazolam, respectively.

**Methods**  
A single-centre, open-label, Phase I, DDI study in healthy adult volunteers (N = 20; male/female = 10/10). Day 1: A single dose of probe substrates (cocktail approach; caffeine (100 mg), omeprazole (20 mg), dextromethorphan (30 mg), and midazolam (2 mg)) was administered; PK assessments were conducted over 48 h.

**Results**  
Day 2–7: 6-day washout period. Day 8: a single dose of osilodrostat 50 mg was administered followed by a single dose of probe substrates 0.5 h later. PK assessments were conducted over 48 h.

**Conclusions**  
Inosilodrostat (LCI699) is a low drug–drug interaction potential, with no new safety signals reported during long-term treatment. Results from this study suggest that osilodrostat may be effective in the long-term treatment of Cushing’s disease.

**Disclosure**  
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A specific nursing educational programme in patients with Cushing’s syndrome

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Context
Cushing’s syndrome (CS) is a rare endocrine disease, due to cortisol hypersecretion. CS patients have several comorbidities, often still present after biochemical cure. There are no specific nursing healthcare programs to address this disease and achieve improved health related quality of life (HRQoL). Thus, an educational nursing intervention in these patients, through the development and promotion of specific educational tools, appears to be justified.

Objective
To assess the effectiveness of an educational nursing programme in CS patients to improve HRQoL, clinical parameters, level of pain and physical activity, patterns of rest and use of health resources.

Patient and methods
A prospective, randomized study was conducted in two reference hospitals for CS. Sixty-one patients (mean age 47 ± 12.7 years, 83.6% females) were enrolled and divided into two groups: an ‘intervention’ group where educational sessions were performed over nine months and a ‘control’ group, without these sessions. Specific questionnaires were used at the beginning and end of the study.

Results
After the educational sessions, the intervention group had a better score in Pain QoL (P < 0.003), improved level of pain (P < 0.05), physical activity (P < 0.01) and healthy lifestyle (P < 0.0001) compared to the control group. A correlation between the Cushing QoL questionnaire score and improvement in pain (P < 0.05), physical activity (P < 0.01) and sleep (P < 0.01) was observed.

Conclusions
This educational nursing program improved HRQoL, physical activity, healthy lifestyle and promoted adherence to therapy and better sleep patterns in CS patients, reducing health resources consumption. The brief nature of the programme makes it a good candidate to be used in patients with CS.

Disclosure
Mª Antonia Martínez-Momblán received an unrestricted grant from Novartis as an investigator initiated study. The other authors have nothing to disclose.

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Neurosurgey outcome in patients with Cushing’s disease with and without visualised pituitary adenoma on MRI, who underwent inferior petrosal sinus sampling

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Objective
To estimate the outcome of neurosurgery in patients with Cushing’s disease (CD) with and without pituitary adenoma visualisation on MRI.

Material and methods
Patients with confirmed CD (November 2008 – December 2014) by both inferior petrosal sinus sampling (IPSS) and histological evaluation after neurosurgery were enrolled into the study. Subjects were referred for IPSS because of adenoma ≤ 6 mm, 29 patients underwent IPSS due to negative for CD non-invasive tests. After the first neurosurgery remission was not achieved in 15 (29.4%) patients out of 51 without visualised adenoma on MRI, and in 9 (17.3%) cases out of 62 patients with visualised pituitary adenoma P = 0.066 OR: 2.45 (0.97 – 6.21).

Conclusion
Remission rate after neurosurgery does not statistically significant differ between patients with CD with vs. non visualised pituitary adenoma on MRI and other patients with CD initially referred for IPSS.

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Thyroid - diagnosis

Evaluation of strain elastography for differentiation of thyroid nodules: results of a prospective multicentre study

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Introduction
Work-up of thyroid nodules remains challenging. At present, many patients with thyroid nodules are referred to surgery for diagnostic rather than therapeutic purposes. Therefore, the value of non-invasive diagnostic methods to optimize the selection of patients for surgery is needed. Strain elastography (SE) enables the determination of tissue elasticity and has shown promising results for the differentiation of thyroid nodules.

Methods
The aim of the present study was to evaluate the value of SE in a prospective multicentre study. A sample size calculation was performed when planning the study and the study was registered at clinical-trials.com. The study was approved by the local ethical committees of all participating centres, and written informed consent was obtained from all patients. All patients received an ultrasound (US) of the thyroid gland including colour doppler US and TIRADS classification. In addition all nodules were evaluated by strain elastography (Hitachi Medical System) using qualitative image interpretation of colour distribution (elastography score (ES) 1–4), strain value and strain ratio. Cytology and/or histology was used as reference method for all benign and histology only for all malignant nodules.

Results
Overall, 604 patients with 659 thyroid nodules (570 benign, 89 malignant) from six centres across Germany were included in the final analysis. Sensitivity, specificity, PPV, NPV, +LR and −LR were 85%, 74%, 86%, 4%, 0.9 for colour Doppler vascularization pattern 3–4; 79%, 40%, 92%, 17%, 1.3 for TIRADS; 69%, 74%, 92%, 36%, 2.66 for SE-ES; 58%, 81%, 92%, 32%, 3.0 for SE-strain value (cut-off 0.165); 60%, 78%, 92%, 31%, 2.7 for SE- strain ratio (cut-off 0.376), respectively. The diagnostic accuracies were 80% for TIRADS, 75% for SE-ES, 72% for SE-strain value, and 71% for strain ratio, respectively. No significant difference was found between these diagnostic accuracies.

Conclusions
Strain elastography as an additional ultrasound tool improves the diagnostic value of ultrasound for the exclusion of malignant thyroid nodules. Qualitative and semiquantitative elastography scores are comparable good.

Disclosure
This work was supported by Hitachi Medical Systems by providing ultrasound machines to some participating centers.

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GP.23.02
Accuracy of sentinel lymph node biopsy in papillary thyroid carcinoma in decision for selective lateral neck dissection
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Introduction
The incidence of occult lymph node metastases (LNM) in papillary thyroid carcinoma (PTC) reaches 80%, still their surgical management in clinically node negative (cN0) patients remains controversial and ranges from ‘wait and see’ to prophylactic dissections of both central and lateral neck compartments. This encouraged some authors to apply the concept of sentinel lymph node biopsy (SLNB) in PTC. Our aim is to investigate if SLNB using methylene blue dye is accurate in detection of LNM in lateral neck compartment and may help in decision for selective modified lateral neck dissection in cN0 patients with PTC.

Study design
Study included 153 cN0 patients with PTC. All underwent total thyroidectomy with prophylactic central neck dissection and SLNB of lateral lymph nodes using methylene blue dye with selective modified lateral neck dissection in metastatic SLNs.

Results
Over 80% of patients had pT1 tumours, including 57% of microcarcinoma. Neck LNM were histologically verified in 40.9% of cases. Central neck compartment LNM were predictive for lateral LNM in 80.5% of cases. Predictive factors for LNM were: male gender, patients younger than 45 years, tumours greater than 1 cm, capsular and vascular tumour invasion. Our method enabled detection of metastases in 21% of SLN in lateral neck compartment, which were over 50% predictive of metastasis to other lateral lymph nodes. SLN identification rate (IR) was 91.81%. Sensitivity, specificity and positive and negative predictive value were 85.7, 96.7, 88.3 and 95.9% respectively. The overall accuracy of the method was 94.3%, with 91.2% probability of repeating the results in the second specimen (ROC AUC, 95% CI: 84.2–98.3%).

Conclusion
The proposed method of SLN biopsy is feasible, safe and accurate in detection of additional LNM in the lateral neck compartment and may help in decision for selective modified lateral neck dissection in cN0 patients with PTC.

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GP.23.03
Incremental value of serial preablative thyroglobulin measurements in identifying distant metastatic differentiated thyroid cancer
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Introduction
Thyroglobulin plays a vital role in the follow-up of patients with differentiated thyroid carcinoma (DTC) after thyroidectomy combined with radioiodine (RAI) ablation. As to preablative stimulated thyroglobulin (ps-Tg), though several studies have manifested its potential in identifying distant metastatic DTC (DM-DTC), it remains unclear whether a single ps-Tg is sufficient for predicting DM-DTC. This retrospective study was aimed to evaluate the utility of serial ps-Tg measurements in identifying DM-DTC.

Methods
A series of ps-Tg thyroid-stimulating hormone (TSH) and anti-Tg antibody (TgAb) was measured in 317 consecutive DTC patients before RAI administration, among which data collected at the first time were marked as Tg1, TSH1 and TgAb1, respectively, while as Tg2, TSH2 and TgAb2 at the last time. Patients were divided into two groups as M1 (n = 72) and M0 (n = 245) according to the presence of DM or not. Parameters derived from the change in ps-Tg including ΔTg (Tg2-Tg1), ΔTg’ (Tg2/TSH2-Tg1/TSH1) and ΔTg/ΔTSH (ΔTg/(TSH2-TSH1)) were calculated and further combined with an actual or corrected value of ps-Tg (Tg1, Tg2, Tg1/TSH1 or Tg2/TSH2). All the independent and combined parameters were tested for diagnostic performance in identifying DM-DTC.

Results
Higher Tg1, Tg2, Tg1/TSH1, Tg2/TSH2 and wider amplitudes of ΔTg, ΔTg’, ΔTg/ΔTSH were observed in M1 (all P < 0.01). Tg2 and Tg2/TSH2, with corresponding areas under ROC curves (AUC) of both 0.947, were more accurate than Tg1 and Tg1/TSH1. ΔTg/ΔTSH manifested the highest accuracy (88.64%) and specificity (90.20%) among the three parameters of preablative changes, with a diagnostic range of −0.40–0.41 ng/mL. Moreover, the diagnostic performance was further improved with a larger AUC (0.951) by combining ΔTg/ΔTSH with Tg2/TSH2.

Conclusions
Serial ps-Tg measurements hold incremental value in identifying DM-DTC. ΔTg/ΔTSH in conjunction with Tg2/TSH2 is a favorable indicator for DM-DTC as well as a feasible approach to assist in preablative assessment and decision-making.

Disclosure
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GP.23.04
Impact of antithrombotic and/or anticoagulant treatment in cytological results of thyroid fine-needle biopsy
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Introduction
Fine-needle aspiration biopsy (FNAB) of the thyroid gland is an accurate diagnostic test used routinely in the initial evaluation of nodular thyroid disease. A sizeable subset of patients are found to be taking antithrombotic and/or anticoagulant (AT/AC) medications. This creates a dilemma for the endocrinologist, who must weigh the risk of withholding these medications (and the associated potential benefit of diagnosis) against the perceived increased risk of iatrogenic bleeding.

Material and methods
We examined records of patients who underwent ultrasound-guided fine needle aspiration biopsy (US-FNAB) of thyroid nodules from the whole period 2012–2014, in order to determine whether there was a significantly increased incidence of bleeding complications in patients on AT/AC medications (test group) compared to patients not receiving AT/AC therapy (control group). All the studies were performed by the same experienced operator and cytopathologist team. The χ² test was used to assess statistically significant differences between test group and control group.

Results
A total of 83 patients (9.09%) were taking AT/AC medications without preprocedural interruption. Five US-FNAB-related hematomas (0.5%) occurred. Three hematomas developed in patients on AT/AC treatment, and two hematomas developed in patients who did not take AT/AC medications (P = 0.0014). Twenty-four patients in the test group (40.6%) were labelled as ‘nondiagnostic’ cytology, vs 84 patients in the control group (10.1%) (P < 0.0001).

Conclusion
Our results revealed an increased incidence in ‘non diagnostic’ or ‘unsatisfactory’ cytology in patients on AT/AC treatment, finding not described in previous studies until now. This could be related to a higher rate of pathological artifacts associated with lower blood coagulability. Our results also showed an increased bleeding risk in patients on AT/AC treatment. Despite this fact, most of studies argue that US-FNAB may be performed safely on a patient taking standard doses of aspirin or anticoagulants.

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**GP.23.05**

Comparison of cytopathology vs thyroglobulin measurement in fine-needle aspiration biopsy in patients with differentiated thyroid cancer

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**Aim**
Differentiated thyroid cancer (DTC) is the most commonly seen endocrinological tumour. During the follow up of DTC, serum thyroglobulin (TG) levels, neck ultrasound, fine needle aspiration biopsy (FNAB) of the suspicious lymph nodes are important tools. TG washout of the suspicious lymph node as well as the FNAB can detect metastasis and recurrences earlier. In this study we aimed to show the diagnostic role of TG washout of suspicious lymph node FNAB which is not routinely done.

**Methods**
Totally 80 DTC patients that had suspicious lymph nodes during the follow up after thyroidectomy and radioactive ablation were retrospectively evaluated. All of patients' FNAB and TG washouts were done. Patients that underwent an operation thereafter were also evaluated according to the pathology.

**Results**
Totally 80 papillary thyroid cancer (PTC) patients, 91 lymph nodes were evaluated. 22 patients were operated, the rest of the patients that needed operation did not accepted operation. In 16 patients, FNAB was malign and TG washout was positive and all these two predicted the operation pathology which was malignant. In three patients FNAB was suspicious, TG washouts were negative but operation pathology was benign, TG washout predicted the true benign pathology in these three patients. In three patients FNAB was benign but TG washouts were positive and operation pathology was malign and TG washout predicted the pathology. TG washout predicted benign disease in three and malign disease in three patients which FNAB showed the contrary.

**Conclusion**
Our study showed that TG washout can be used with adjunct to FNAB during the follow up of DTC patients that had already operated and received radioactive ablation especially in patients with suspicious lymph nodes on follow up neck ultrasound. TG washout can aid in diagnosing recurrences and metastasis earlier and can increase the survey of the disease.

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**GP.23.06**

FDG-avidity of thyroid cancer does not predict clinical aggressiveness in PET incidentaloma

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**Objective**
18F-FDG-avid differentiated thyroid cancers (DTC) have been known to behave more aggressively, especially in metastatic sites (flip-flop phenomenon). However, the clinical behaviour of DTC detected incidentally by FDG-PET (PET incidentaloma) has been sparsely reported. We wanted to know whether flip-flop phenomenon is applicable in PET incidentaloma.

**Methods**
165 DTC patients who underwent thyroid surgery and had pre-operative FDG-PET examination at Chonnam National University Hwasun Hospital between January 2006 and August 2013 were included in the study. We compare the clinical characteristics between screening PET-CT group (PET incidentaloma) and staging PET-CT group.

**Results**
129 DTC patients were FDG-avid and 36 patients non-FDG-avid. FDG avid PTC is more aggressive than FDG non-avid PTC on the clinico-pathologic findings. After removal of high-risk group (staging PET-CT group), thyroid PET-CT incidentaloma patients (n = 107) were compared according to FDG avidity. Among thyroid PET-CT incidentaloma patients, FDG avid PTC group (n = 75) revealed larger tumour size (0.97 ± 0.52 vs 0.61 ± 0.35, P = 0.001), but extrathyroidal invasion (ETI), cervical lymph node metastasis, and distant metastasis is not different between FDG avid PTC group and FDG non-avid PTC group. A cumulative risk of cervical lymph node metastasis according to primary tumour size of FDG avid PTC group is not different from those of FDG non-avid PTC group (P = 0.394).

**Conclusions**
DTC detected with FDG-avidity do not seem to behave aggressively, based on initial operative findings. FDG-avidity of DTC does not add to conventional risk factor assessment for initial therapeutic decision.

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**GP.23.07**

Immunohistochemical tool for the diagnosis of benign and malignant follicular tumours

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**Introduction**
Follicular tumours of the thyroid gland include benign follicular adenomas, follicular carcinomas and the follicular variant of papillary carcinoma. Although, molecular markers are a promising area of research to differentiate thyroid neoplasms, there is ample room for improvement in the research and clinical applications in this field. Furthermore, the final diagnosis requires thyroid lobectomy. The present study examined whether a differential protein expression could provide an accurate tool to improve diagnosis in these tumours.

**Design**
The expression of 19 proteins was evaluated in 125 surgically removed thyroid tumours including 81 follicular adenomas (FA) and 44 malignant tumours (nine follicular carcinomas (FTC) and 35 follicular variant of papillary carcinomas (FVPTC)). Classification trees and scoring systems were constructed based on protein expression to generate models that could allow a differential diagnosis between benign and malignant tumours. Forty hyperplastic nodules (HN) were used to test the goodness of fitness of the generated models.

**Results**
The classification tree that better discriminated between benign and malignant nodules was APLP2 (n = 0), RRM2 (n = 5), PRClc (n = 40), APLP2c (n = 15), and SIAH1 (n = 5), with a sensitivity of 100% and a specificity of 98.8%. In HN, the sensitivity was 94.8%. The punctuation system model 4×(APLP2 (n = 0)) + 2×(RRM2 (n > 5)) + 1×(PRClc (n = 40)) reached a sensitivity of 100% and a specificity of 71.3%.

**Conclusion**
Our findings support the potential of these models to improve not only the diagnosis of follicular thyroid tumours but also, the management and wellness of patients by reducing the number of exploratory surgeries. We are currently validating these results in an independent series.

**Disclosure**
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**GP.23.08**

Clinical characteristics in sporadic and familial medullary thyroid carcinomas: worse outcome in sporadic cases even when disease stage at diagnosis is similar

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**Objectives**
Medullary thyroid carcinoma (MTC) has varying clinical course with familial cases (sMTC) diagnosed earlier than sporadic ones (sMTC). We examined the presentation of these entities in our centre.

**Methods**
223 MTC patients (familial: 42.6%, males: 36.8%) were followed for 0.9–30 years (mean 6.23±5.9, median 4.0 years), 44 (19.7%) IMTC patients were operated after genetic screening.

**Results**
Median age at diagnosis was for IMTC: 32.4±16.3 years (range 4–73) and for sMTC: 52.4±13.6 years (range 16–81, P < 0.001). This difference remained when cases diagnosed after genetic screening were excluded (P = 0.001). IMTC was more frequent in women than men (48.2% vs 32.9%, P < 0.008). Capsular invasion, lymph node invasion, distant metastasis at diagnosis was similar. The size of sMTCs was more frequently ≥1.5 cm (P = 0.012), Stage at diagnosis was more favorable in IMTCs (stages I and II: 60.4% vs 51.2%, stage III: 8.8% vs 23.2%, and stage IV: 42.1% vs 57.9%, P = 0.021). Preoperative and postoperative calcitonin levels were significantly lower in IMTCs. IMTC had more frequently remission (62.9% vs 49.2%) and less frequently progressive disease (9% vs 36.3%, P < 0.001).

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After excluding patients diagnosed through genetic screening, no difference in stage at diagnosis was observed. Tumour size and postoperative calciﬁtonin levels did not differ. Outcome was more favorable in IMTC compared to sporadic (remission: 56.3% vs 48.8%, stable: 29.2% vs 14.6%, and disease progression: 14.6% vs 36.6%, P = 0.008). The 10-year probability of lack of progression of disease differed signiﬁcantly between familial and sporadic MTCs (85.4% vs 63.4%, Kaplan–Meier analysis, \( \chi^2 = 19.01, P < 0.001 \)).

Conclusions
After excluding those diagnosed through genetic screening, although stage at diagnosis is currently similar and does not differ between familial and sporadic cases, disease outcome remains worse in sporadic MTCs. Women may have increased awareness for genetic screening in familial cases.

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GP.23.09
Low/undetectable pre-ablation thyroglobulin in well-differentiated thyroid cancer patients with positive post-ablative 131I whole body scan: causes and consequences
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Introduction
In patients with well-differentiated thyroid cancer (DTC) low/undetectable thyroglobulin (Tg) at time of remnant ablation usually reﬂects a complete previous surgery. However, in a small percentage (6.3–16%) it can represent false negative values.

Objectives
Evaluate the frequency of patients with low/undetectable Tg at time of remnant ablation with locoregional or distant lesions at post-ablative 131I whole body scan (WBS) and the inﬂuence of Tg levels in long-term outcome.

Methods
Retrospective analysis of all patients with DTC submitted to ablative 131I treatment in our centre. Included: patients with a stimulated Tg > 30 mIU/ml after thyroid hormone withdrawal or with a follow-up > 6 months. Statistical analysis: SPSS (21).

Results
Of 967 patients, 211 (21.8%) were included (178f; 33m). Ninety-two (43.6%) presented anti-Tg antibodies. Only patients with negative anti-Tg antibodies (n = 119) were considered at subsequent analysis. In those, Tg was lower if lymphocytic inﬁltrate (P < 0.05) or abundant solid areas (P < 0.05) present at histopathological evaluation. Post-ablative 131I WBS showed thyroid bed (73.3%), locoregional (5.9% unilateral and 16.8% bilateral), supraventricular (0.8%), mediastinal (1.6%), and pulmonary (1.6%) uptake. During a follow-up of 8 ± 4.8 years, 17 (14.3%) patients showed persistence/recurrence of the disease: eight local and nine distant. The probability of persistence/recurrence was signiﬁcantly higher if lymph node metastasis (OR = 11.8; P < 0.001) or extrathyroidal uptake at post-ablative 131I WBS (OR = 20.8; P < 0.001). Disease-free survival was inversely correlated with Tg (p = −0.59; P < 0.01), being signiﬁcantly higher in patients presenting undetectable Tg (P < 0.005).

Conclusion
A ﬁfth of DTC patients presented low/undetectable Tg at time of remnant ablation with uptake (locoregional or distant) at post-ablative 131I WBS. In about half was justiﬁed by anti-Tg antibodies. In the others, may be related to the presence of microscopic lesions or speciﬁc histopathological features. In these patients, low/undetectable Tg did not exclude risk of persistence/recurrence, but it seems related with disease-free survival. This study also highlights the importance of post-ablative 131I WBS in the evaluation of these patients.

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Thyroid – genetics

GP.24.01
Prox1 transcription factor is differentially expressed in thyroid cancer and contributes to the regulation of invasion and migration of thyroid cancer cells
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Introduction
The differentiated thyroid cancer (DTC) is the most frequent endocrine malignancy with the incidence increasing worldwide. Although, DTCs are considered to be mostly indolent lesions, the proportion of patients develop metastases. Therefore, identiﬁcation of molecular factors that are involved in thyroid tumour progression might help to better understand the mechanism of thyroid cancer metastasis. In the present study we examine the role of the transcription factor prospero homeobox 1 (Prox1) in DTC biology. Prox1 is the nuclear transcription factor expressed speciﬁcally in LEC cells and as recently shown, also in several human cancers.

Methods
We performed studies using follicular and papillary thyroid cancer derived cell lines. The Prox1 protein and transcript expression levels and its localization were determined using molecular biology methods: Q-RT-PCR, gene silencing, western blot, and immunocytochemistry. To determine Prox1 role in regulating the hallmarks of malignant cell phenotype we analysed migration, invasion, anchorage-independent growth, proliferation, cell cycle, apoptosis, and adhesion upon Prox1 gene silencing.

Results
We observed signiﬁcant difference in the Prox1 expression between FTC and PTC derived cancer cell lines. Prox1 transcript and protein levels were overexpressed in follicular cancer cell lines FTC133 and CGTH when compared with PTC cell lines. Moreover, the protein was localized in the nucleus or both the nucleus and cytoplasm respectively. RNAi knockdown of Prox1 suppressed cellular migration, invasion and anchorage independent growth of FTC-133 cells, whereas proliferation, cell cycle and adhesion were unchanged. Moreover, Prox1 down regulation modiﬁed of FTC133 cells shape by actin cytoskeleton reorganization.

Conclusion
Our data suggest an important role for transcription factor Prox1 in i) the regulation of hallmarks of the malignant cell phenotype as migration and invasive capacity and ii) in the actin cytoskeleton remodelling in thyroid cancer cells. Further on-going studies will clarify the role of Prox1 in thyroid cancer cells dissemination.

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GP.24.02
In papillary thyroid cancer TERT promoter mutations have a worst impact on outcome than BRAF mutations
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TERT promoter mutations (chr5: 1 295 228C > T and chr5: 1 295 250C > T) were recently described in thyroid tumors, with a prevalence ranging 8–25% in papillary thyroid cancer (PTC). We and others reported that these mutations strongly associate with a poor outcome in differentiated thyroid cancers. Aim of...
the present study was to further investigate the prognostic role of both TERT promoter (TERTprom) and BRAF(V600E) mutations in a larger series of 216 PTCs with a long follow-up (median: 77 months). We also evaluated the possible additive effect on the outcome of the coexistence of the two genetic alterations. Genetic data were obtained by direct sequencing and were correlated with full clinical data. The prevalence of TERTprom and of BRAF(V600E) was 12 and 35% respectively. Ten cases (5%) harbored both TERTprom and BRAF(V600E). Cases with a TERTprom alone, but not those with BRAF(V600E) alone, were significantly associated with older age at diagnosis and poorer outcome (P = 0.04 for both). No differences in the outcome were noted between cases with the TERTprom alone or with the coexistence of TERTprom and BRAF(V600E). In conclusion, TERT mutations were found to have a 12% prevalence in PTCs and were confirmed to be a major indicator of poor prognosis. On the other hand, BRAF(V600E) was not associated with the outcome, consistent with data previously obtained in our series. Moreover, the outcome was not different among tumors with isolated TERTprom and those with coexistent mutations (TERTprom/BRAF(V600E)), indicating that BRAF(V600E) does not confer an additional effect in the disease persistence.

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GP 24.03
Evaluation of genetic background of sporadic medullary thyroid carcinomas

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Objectives
Although, almost all patients with inherited medullary thyroid carcinomas (MTC) harboured RET proto-oncogene mutation, in patients with sporadic MTC mutations in RET are detected only in half of cases. Thus still unknown genetic causes are responsible for half of sporadic MTC and it is necessary to search for another mutations.

Methods
DNAs from fresh frozen thyroid tissues of 27 sporadic MTC were extracted. The next-generation sequencing (NGS) approach was used to target 175 exonic regions of 26 genes involved in tumors. The samples were prepared using a TruSeq Tumor panel (Illumina) and sequenced with a MiSeq sequencer regions of 26 genes involved in tumors. The samples were prepared using a next-generation sequencing (NGS) approach was used to target 175 exonic regions of 26 genes involved in tumors. The samples were prepared using a TruSeq Tumor panel (Illumina) and sequenced with a MiSeq sequencer.

Results
Among molecular markers proposed to improve diagnosis of thyroid nodules, TERT mutational analysis on thyroid core needle biopsy

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Introduction
Among molecular markers proposed to improve diagnosis of thyroid nodules, mutations in telomerase reverse transcriptase promoter (TERT) promoter have been correlated to malignant tumors with highest recurrence and decreased patient’s survival. This suggest an important role of TERT mutational analysis in the clinical diagnosis and management of thyroid cancer patients. In this study, we investigate the potential use of core needle biopsy (CNB) for the preoperative assessment of TERT mutational status and we correlate TERT status with BRAF mutation, definitive histology and post-operative TNM staging of the neoplasia.

Methods
The series included 50 thyroid nodules, retrospectively selected among 187 patients who underwent CNB due to an inconclusive fine-needle aspirate (FNA) report, during last 2 years at two different institutions in Rome. Selected cases consisted of 30 papillary thyroid carcinomas (PTC), one follicular carcinoma (FTC), nine follicular adenomas and hyperplastic nodules did not show the mutation. Mutated cases showed locally invasive PTC with multiple lymph-node metastases and, in one patient, with lung metastasis. All TERT mutated cases showed concomitant V600 BRAF mutation.
Conclusions
The present study demonstrates the feasibility of TERT promoter mutational analysis on thyroid CNB. This methodology consents to identify tumors with a worse outcome at the preoperative time on specimens evaluated for quality and representativeness. This information might be used to individualise treatment decisions, surgical options and follow-up design.

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GP.24.06
Gene expression profiling in differentiated thyroid carcinoma
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Thyroid carcinoma is the most common endocrine malignancy and represents ~1% of all types of human cancer.

Objective
As the molecular pathogenesis of thyroid cancer still remains to be clarified, the goal of our study was to find new molecular markers that could improve the diagnoses, follow-up protocols, treatment outcome, prognosis and the quality of life of differentiated thyroid cancer patients.

Subjects and methods
Matched tumour and normal thyroid tissue samples were obtained from patients that have surgical cure for differentiated thyroid carcinoma after they gave their informed consent. RNA was extracted using the RNeasy Mini Kit from Qiagen and the quality was checked with the Infinite 200 NanoQuant (Tecan) and with the 2100 Bioanalyzer (Agilent). 24 samples with RIN > 7 were chosen for microarray gene expression analysis (six with classical papillary thyroid carcinoma and six with papillary thyroid carcinoma follicular variant). Microarray analysis was performed following Agilent One-Color Microarray-Based Gene Expression protocol, ver 6.6, using SurePrint G3 Human Gene Expression arrays 8x60K v2.

Results
Using GeneSpring ver 12, we identified 25 genes and two long intergenic non-protein coding RNA (lincRNA 1140 and BROAD Institute lincRNA 9114) using GeneSpring ver 12, we identified 25 genes and two long intergenic non-protein coding RNA (lincRNA 1140 and BROAD Institute lincRNA 9114) down regulated in the tumour tissue compared with the normal one, P value <0.05 and fold change ≥2. When accounting for the two thyroid cancer types studied, we identified three genes up-regulated (COL13A1, ED2AR, and KLHDC8A) and eight down regulated (SLITRK5, CCL21, TFPI, TBX1, LOC389033, ADH1C, MMRN1, and F10) in both subtypes. The level of gene expression deregulation is much higher in the case of classical papillary thyroid carcinoma.

Conclusion
Gene expression is altered in papillary thyroid carcinoma. Our study identified three hyper-expressed genes and eight genes with low expression in tumoural tissue compared to normal one. Further studies are undergoing for gene expression data validation by qPCR.

Disclosure
This work was supported by UEFISCDI (grant number PN-II-PT-PCCA-2011-3.2, 135/2012).

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GP.24.07
Combination of serum miRNA-190 and -95 is a powerful non-invasive tool in the differential diagnosis of thyroid nodules: preliminary data of a prospective series
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Background
MicroRNAs (miRNAs) are small non-protein encoding RNAs which negatively regulate gene expression. Tissue miRNA profiles may be useful to distinguish benign from malignant lesions. Recently, we have identified in the serum of a retrospective series of patients, with benign nodular goiter (n=80) and papillary thyroid cancer (PTC: n=79), two miRNAs (-190 and -95) that in combination (providing the risk of malignancy defined as pmRNA) allow the differential diagnosis of thyroid nodules with great accuracy. This study was aimed to confirm the diagnostic accuracy of miRNA-190 and -95 in a prospective series of patients.

Methods
Blood samples were collected from 126 consecutive patients undergoing fine-needle aspiration cytology at our Institute. miRNAs were extracted from serum using the miRNeasy Serum/Plasma Kit (Qiagen), and reverse-transcribed using Megaplex Human microRNA RT primers pools v2.1 (Life Technologies). cDNA was then pre-amplified. Relative expression quantification was evaluated by the comparative cycle threshold (CT) method (2^(-Ct)) (Rotor-gene Q, Qiagen). Endogenous miRNA-16 and miRNA-451 were selected as reference to normalize miRNA expression values.

Results
Based on cytology (following BTA guideline): the lesions were benign (Thy2) in 85/121 (70.2%) cases, suspicious for malignancy or malignant (Thy4/5) in 14/121 (11.6%), indeterminate (Thy3) in 16/121 (13.2%), and non diagnostic (Thy1) in 6/121 (5%). A subgroup of 48 patients underwent surgery and the lesions at histology were benign in 30/48 (62.5%) cases and malignant in 18/48 (37.5%). PmiRNA showed a high sensitivity (84%), specificity (93.5%), and diagnostic accuracy (90%) in PTC diagnosis. Moreover, by applying pmiRNA, we could have avoided two out of three unnecessary surgeries in patients with Thy3 cytology.

Conclusions
These preliminary data confirm that pmiRNA may be useful as a non-invasive diagnostic tool for the differential diagnosis of thyroid nodules, particularly in case of indeterminate lesions where pmRNA role is promising but further studies are warranted.

Disclosure
PRIN No. 2010RNY8T_001; MOH-GR-2010-2324154.

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GP.24.08
Identification of a LIN28B/miR-30a axis controlling thyroid cell invasion and proliferation
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The oncofetal microRNA binding protein LIN28B plays an important role in differentiation and cancer progression. Lin28B induces epithelial-mesenchymal transition, and it is considered as a bad prognostic marker in several tumours. The aim of this work was to study the effect and regulation of LIN28B on the thyroid cancer progression process. In a first approximation a miRNA targets computational predictions were performed with miRNA algorithm and we found that among others the miR-30a binds to the 3′ UTR of LIN28B. As previous results, obtained by next-generation sequencing expression analysis, performed in our laboratory showed that miR-30a is one of the most significantly miR subexpressed in thyroid cancer, we decided to focus on its role over LIN28B. miR-30a expression vector was transfected in 8505c and Cal62 cells; LIN28B in NThy-ori thyroid cells; and reporter construct containing LIN28B 3′ UTR in 293T cells. miR-30a expression values.

Combination of serum miRNA-190 and -95 is a powerful non-invasive tool in the differential diagnosis of thyroid nodules: preliminary data of a prospective series
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Background
MicroRNAs (miRNAs) are small non-protein encoding RNAs which negatively regulate gene expression. Tissue miRNA profiles may be useful to distinguish benign from malignant lesions. Recently, we have identified in the serum of a
Thyroid - nodule

GP.25.01

Long-term results of US-guided high-intensity focused ultrasound treatment of benign thyroid nodules
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Introduction
Nodules can be detected by ultrasound (US) in 20–30% of unscreened populations. Various non-surgical techniques such as laser and radiofrequency ablation have been developed to reduce thyroid nodule size. High-intensity focused ultrasound (HIFU) ablation is a new, non-invasive method that has been shown recently. The aim of our study was to assess the long-term efficacy and safety of US-guided HIFU treatment of benign solid thyroid nodules.

Methods
In our prospective study, 14 patients, mean age 47.6 ± 11.2 years, were treated with US-guided HIFU system (EchoPulse, Theraclick) in one session and under conscious sedation. Thyroid nodule volume and volume reduction were established at baseline, 1, 3, 6, and 12 months after treatment. Adverse events were evaluated and pain related to treatment was rated on 0–100 mm visual analogue scale (VAS). Written informed consent was acquired from all patients.

Results
The mean energy applied per nodule volume was 3.7 ± 1.5 KJ/ml. The mean nodule volume decreased from 4.97 ± 2.54 to 3.56 ± 2.01 ml at 1 month, 2.84 ± 1.95 ml at 3 months, 2.55 ± 2.23 ml at 6 months, and reaching 2.35 ± 2.34 ml at 12 months follow-up. The mean nodule reduction was 29.5 ± 15.9% at 1 month (P < 0.001), 46.2 ± 18.5% (P < 0.001) at 3 months, and 52.8 ± 23.3% (P < 0.001) at 6 months follow-up. By the 12th month, the mean volume reduction was 55.7 ± 27.2% with a maximum of 95.4%. Transient subcutaneous oedema and mild skin redness were observed in two patients. VAS score was 26.1 ± 19.5 mm.

Conclusion
One session HIFU ablation is effective non-invasive treatment for benign thyroid nodules at long-term follow-up, without serious adverse events. Our results indicate that US-guided HIFU might become an alternative to surgery and other minimally invasive treatment techniques.

Disclosure
The device for US-guided HIFU treatment and financial support for the supplies were provided by Theraclick (Paris, France).

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GP.25.02

Thyroid hormones influence the expression of TNF-related apoptosis-inducing ligand
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Background
There is growing evidence supporting TNF-related apoptosis-inducing ligand (TRAIL) involvement in weight and body composition regulation, which are classically influenced by thyroid hormones. This study aimed at investigating the relationship between thyroid hormones and TRAIL.

Methods
Circulating TRAIL was measured in 40 controls, 40 hyperthyroid, and 25 hypothyroid patients before and after their respective treatments. In the subset patients TRAIL gene expression was quantified in peripheral blood mononuclear cells. The effect of T3 and T4 on TRAIL secretion was evaluated in vitro.

Results
TRAIL gene and protein expression significantly increased in hyperthyroid and decreased in hypothyroid patients (vs controls P < 0.05). TRAIL gene and protein expression normalized once euthyroidism was restored (P < 0.05). There was a significant correlation between TRAIL and both T3 and T4 (P < 0.05). Moreover, the changes in body weight and BMI that we found once euthyroidism was restored were significantly correlated to the changes in TRAIL (P < 0.05). The in vitro study showed that T3 stimulated TRAIL release in a dose-dependent manner.

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Conclusion
These findings are consistent with the view that TRAIL might be involved in body weight regulation. In addition, this work sheds light on the possibility that TRAIL might be one of the molecules mediating thyroid hormone peripheral effects.

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GP.25.03

Malignancy rate in thyroid nodules with AUS/FLUS cytology in a Cancer Center (Bethesda System for Reporting Thyroid Cytopathology 2009)
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Introduction
The Bethesda System for Reporting Thyroid Cytopathology is the standard for interpreting fine-needle aspiration (FNA) and created a new diagnostic category (III): ‘atypia of undetermined significance/follicular lesion of undetermined significance’ (AUS/FLUS). The risk of malignancy for this category has been ascribed of 5–15% but the real malignancy rate remains unclear and plays a key role to define appropriate management.

Objective
To determine malignancy rate in AUS/FLUS cytologies.

Methods
A total of 126 consecutive patients with AUS/FLUS cytology were retrospectively identified. Results of follow-up, repeat biopsy or surgical pathology were evaluated. Data are presented as frequencies. For comparison we performed Student’s t-test (statistically significance <0.05).

Results
Among 126 patients, 19.0% (24/126) underwent immediate surgery and 50.0% (63/126) repeated FNA. Of patients immediately submitted to surgery, just one was found to have a papillary microcarcinoma inserted into the index lesion, the remaining suspicious nodules being benign. We found five incidental papillary carcinomas (4 < 1 cm). Repeat FNA cytology was unsatisfactory/non-diagnostic in 22.2% (14/63), benign in 17.5% (11/63), AUS/FLUS in 49.2% (31/63), suspicious for malignancy in 9.5% (6/63), and malignant in 1.6% (1/63). Of nodules with two consecutive AUS/FLUS cytologies that were resected (21/31), 23.8% (5/21) were malignant and in one case the lesion couldn’t be determined as benign/malignant. We found no statistical significance regarding nodule size and probability of malignancy of the suspicious nodule (31.7 mm vs 23.0 mm, P = 0.145). Overall, 57 patients underwent surgery to remove the index lesion, yielding a malignancy rate of 19.3% (11/57), as one case couldn’t be classified by histology. Incidental cancers were found in 21.0% (12/57).

Conclusions
Repeating biopsy allows a significant proportion of AUS/FLUS patients to avoid surgery. In our series, nodules with two AUS/FLUS cytologies harbour a malignancy rate of 23.8%. Incidental papillary carcinomas cancers are frequent (21.0%), in accordance with its high prevalence in general population.

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GP.25.04

Evaluation of benign thyroid nodules in a 10-year follow-up
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Introduction
American Thyroid Association recommends that benign thyroid nodules should be revaluated 6–18 months after initial FNA and in case of stability the follow-up should be 3–5 years. However there isn’t any consensus about the periodicity of the follow-up.

Aim
To evaluate the nodules in terms of function, size and malignancy in a 10-year follow-up.
GP.25.05
Sox9 is expressed in thyroid follicular cells and regulates the expression of thyroid differentiation genes
Aristides López-Márquez, Carlos Carrasco-López & Pilar Santisteban

The transcription factor Sox9 is a member of the HMG-box-DNA binding family essential for chordrocyte differentiation, sexual determination, and the maintenance of the stem/progenitor cells in several tissues. Furthermore, Sox9 is involved in the development of endoderm-derived organs. Owing to the endodermic origin of the thyroid, we proposed to study the expression of Sox9 in thyroid follicular cells and its regulation by TSH and TGFβ, two main factors involved in thyroid function. In addition the role of thyroid transcription factors Nkx2-1, FoxE1, and Pax8 was studied. Sox9 mRNA, protein levels and promoter activity were determined by RT-qPCR, western blot, and transient transfection assays of Sox9 promoter reveals the presence of CRE, Smad and thyroid transcription factors binding sites. The results obtained have inhibited it. The TSH effect takes place through cAMP/PKA pathway as forskolin mimics its effects and the PKA inhibitor H89 inhibited the TSH induction. The TSH effect takes place through cAMP/PKA pathway as forskolin mimics its effects and the PKA inhibitor H89 inhibited it. The in silico analysis of Sox9 promoter reveals the presence of CRE, Smad and thyroid transcription factors binding sites. The results obtained have demonstrated that Sox9 promoter is activated by Pax8 and CREB and inhibited by FoxE1. Interestingly, Sox9 activates FoxE1 promoter while inhibited Nkx2-1 and Pax8 ones. These results demonstrate the involvement of Sox9 in the physiology of the thyroid, something hitherto unknown. In addition our results open a new field to study the role of Sox9 in the development and differentiation of the thyroid gland.

Disclosure
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GP.25.06
Clinical outcome of thyroid nodules characterised as atypia of undetermined significance or follicular lesion of undetermined significance (The Bethesda System for Reporting Thyroid Cytopathology) after fine-needle aspiration
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Introduction
‘Atypia of undetermined significance (AUS) or follicular lesion of undetermined significance’ category is established by The Bethesda System for Reporting Thyroid Cytopathology because of the necessity to repeat those thyroid fine-needle aspiration (FNA) results that are not easily classified into the benign, suspicious or malignant categories. In most cases, a repeated FNA results in a more definitive interpretation. Estimated risk of malignancy for an AUS nodule is 5–15%.

Description of methods
A retrospective study was conducted in which those patients with a result of AUS after thyroid FNA between 2010 and 2013 were included. The following variables were considered: proportion of repeated FNA and average time of delay; consistency between repeated and initial FNA; therapeutic management and malignancy incidence rate.

Results
We studied 59 patients (94.9% females, mean age 48.3 ± 14.3 years). FNA was repeated in 76.3% of patients with an average delay of 195.5 ± 125.4 days between both FNA. We achieved the following interpretations: benign 55.6%; persistent AUS 17.8%; follicular neoplasm or suspicious of follicular neoplasm 17.8%; and suspicious for malignancy 8.9%. Thyroidectomy was performed in 55.2% of all patients (40.6% without repeating FNA and 59.4% after repeating FNA). In all cases lobectomy was the selected procedure. The incidence of malignancy was 10.2% of the total sample (18.2% of patients who underwent surgery).

Conclusion
Repeating FNA in patients with a result of ‘atypia of undetermined significance/follicular lesion of undetermined significance’ may contribute to clarify the diagnosis in a large number of cases, helping in the selection of patients who should undergo surgery or alternatively should be observed clinically. The incidence of malignancy detected in our series is consistent with the incidence expected by The Bethesda System.

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GP.25.07
Malignancy risk stratification of thyroid nodules by TIRADS; correlation with cytological results
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Introduction
Knowing that only in 5–15% of FNABs the pathological analysis shows malignancy, enhance diagnostic accuracy is needed. The use of the TIRADS score and a revised version proposed by the British Thyroid Association (BTA) intend to determine if a FNAB should be performed or not in the evaluation of nodular goitre.

Objective
To determine whether an adequate correlation is present between the risk category assigned to the nodules studied under TIRADS/BTA system and cytological results.

Material and methods
To assess the potential of the TIRADS/BTA systems and the degree of concordance with the results derived from FNAB, we designed a retrospective, observational study including 230 patients who underwent thyroid ultrasonography and FNAB. Nodules were classified following the BTA score as benign (U2), probably benign (U3), and suspicious/probably malignant (U4–5). FNAB samples were informed according to the Bethesda classification. Statistical analysis was assessed using the SPSS Statistical Suite (ver 21.0).

Results
Total sample n=230 (valid pairs, n=204); 71.3% females, mean age 59.2 ± 5.6 years. U2 nodules were 76%; in one case (0.7%) the pathological analysis was consistent with malignancy/suspicious for malignancy while the rest of them (99.3%) were informed as benign. U3 nodules comprised 18 nodules, from which 55% had a benign pathological diagnosis, 16.66% likely benign, and 27.77% malignant or suspicious for malignancy. The high-risk group (U4–5) included n=31 (15.1%) nodules: FNAB results showed a malignant/suspicious for malignancy diagnosis in 80.6%, in 12.9% benign, and in 6.4% probably benign. TIRADS score sensitivity was 75% (95% CI: 57.79–87.85%); specificity was 97.62% (95% CI: 94.01–99.33%), with a positive predictive value of 87.1% and a negative predictive value of 94.8%. Cohen’s k coefficient was 0.69 (P<0.001).

Conclusions
The TIRADS/BTA risk scores have proven to be a useful tool to assess thyroid nodules and the need for FNAB, enhancing diagnostic accuracy and resource allocation.

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**Thyroid - hypothyroidism**

**GP.26.01**

**Quality of life in primary hypothyroidism after long-term levothyroxine replacement**

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**Introduction**

There is an increasing awareness for intrinsic imperfections of endocrine replacement therapy affecting general well-being in the long-term. For thyroid hormone, many factors affect the variable responses to hormone replacement, like common genetic variations in deiodinase and thyroid hormone transport proteins, and the inability to provide adequate individual combined T4 and T3 therapy. Despite levothyroxine (L-T4) replacement in primary hypothyroidism and the inability to provide adequate individual combined T4 and T3 therapy, many patients have persistent complaints that have anecdotally been associated to high levels of antibodies against TPO (anti-TPO).

**Aim of the study**

i) To assess quality of life (QoL) in patients with Hashimoto’s thyroiditis (HT) on adequate L-T4 replacement and ii) to explore potential associations with serum TSH and anti-TPO.

**Design**

Cross-sectional, case-control study.

**Patients and controls**

One hundred and twenty patients on long-term L-T4 replacement for HT (mean age 54.0 ± 14.0 years, range 21–75 years) and 60 euthyroid control subjects (aged 53.1 ± 12.4), matched for age, gender, and educational level.

**Methods**

Evaluation of FT4, TSH, and anti-TPO concentrations, and of QoL as measured with the Short Form 36 Health Survey (SF-36) for mental health and vitality in both patients and controls. Patients and controls were subdivided into two age groups: 20–49 years (GR1) and 50–75 years (GR2), with a mean duration of L-T4 replacement of 3.95 and 9.27 years respectively.

**Results**

FT4 and FT3 levels were not different between patients and controls, but TSH was slightly higher in Hashimoto patients (GR1 3.64 ± 2.74 vs 1.93 ± 1.1, P < 0.05 and GR2 3.95 ± 2.84 vs 1.91 ± 0.90, P < 0.05). SF-36 scores in the patients were significantly lower for both age groups compared with controls (patients vs controls): dimension A-physical health GR1: 70.18 ± 15.74 vs 76.54 ± 13.71, P < 0.05; GR2: 55.84 ± 20.2 vs 75.1 ± 12.0, P < 0.01; SF-36 score GR1: 69.8 ± 16.4 vs 76.4 ± 14.1, P < 0.05; GR2: 57.6 ± 21.1 vs 73.7 ± 14.2, P < 0.05. In addition, in both groups anti-TPO levels, but not TSH, were associated with SF-36 scores subscale2 r = −0.208, P = 0.029; subscale3 (body pain) r = −0.268, P = 0.005; subscale4 (general health) r = −0.198, P = 0.038; dimension A r = −0.224, P = 0.019; and SF-36 score r = −0.191, P = 0.046.

**Conclusion**

Patients on long-term L-T4 replacement for HT have impaired QoL that is associated with higher anti-TPO levels.

**Disclosure**

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**GP.26.02**

**High serum IgG4 concentrations in patients with Hashimoto’s thyroiditis**

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**Purpose**

Recent reports strongly suggest that at least some cases of Hashimoto’s thyroiditis (HT) may be closely associated with IgG4-related disease. In the present study we aimed to find out, whether the measurement of serum IgG4 allows for an identification of distinct types of HT, with different clinical, sonographic and serologic characteristics.

**Methods**

The group studied consisted of 53 patients with HT and 28 healthy individuals. All the participants underwent thyroid ultrasonography and body composition analysis. Serum concentrations of IgG4, TSH, anti-peroxidase antibodies (TPOAb), anti-TSH receptor antibodies, T NFα, TGF-β1, Fas ligand, TRAIL, and chemokines: CXCL9, CXCL11, and CXCL10 were also measured by commercial ELISA or RIA.

**Results**

The group with IgG4 level > 135 IU/ml accounted for 32.5% of the patients. The percentage of male patients was 7.5% in the subgroup with normal IgG4 and 18.2% in the subgroup with high IgG4 concentration. The signs of fibrosis were present in 27.0% of the high IgG4 patients and in 9.1% of the normal-IgG4 group. The patients with elevated IgG4 required higher doses of l-thyroxine, had significantly lower level of TPOAb (P = 0.02) than the non-IgG4-HT individuals, and higher TNFα level in comparison with the controls (P = 0.01); whereas the concentrations of other cytokines/chemokines and apoptotic markers did not differ between the groups studied.

**Conclusions**

Our results suggest that the measurement of serum IgG4 allows for an early identification of patients who require higher doses of l-thyroxine. A relatively low TPOAb level and the absence of co-existing autoimmune diseases may suggest a distinct pathomechanism of this type of thyroiditis.

**Disclosure**

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**GP.26.03**

**Adverse metabolic correlations relate to free T3 levels in subclinical hypothyroidism: common FOXE1 polymorphisms associate with blood pressure**

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**Introduction**

The effects of mild subclinical hypothyroidism (SH; TSH <10 mU/L) on metabolic outcomes are unclear. This may relate to differences in aetiology, including thyroid autoimmunity or genetic factors such as TSH-receptor mutations (TSHR-M) and FOXE1 polyalanine tract length (FOX-E1–PTL) polymorphisms, which are associated with altered thyroid function. We hypothesised that the metabolic manifestations of SH may depend upon its aetiology.

**Aims**

i) To establish whether free T₄, free T₃, or TSH associate with metabolic parameters and blood pressure (BP) in SH. ii) To investigate whether SH aetiology has a differential effect on metabolic parameters and BP.

**Methods**

A total of 288 adults with primary untreated SH (TSH ≥5 mU/L) were recruited and underwent a medical/lifestyle history, resting BP and BMI measurement, genetic evaluation (for TSHR-M and FOXE1–PTL status), thyroid function, anti-TPO antibody measurement, and metabolic assessments (HOMA-IR, full lipid profile). Associations were examined using stepwise multivariate regression analyses.

**Results**

TSH showed a small positive association with free T₃ (R = 0.06, P = 0.01) and a negative association with free T₄ (R = −1.1, P < 0.001) but no association with metabolic factors or BP. Free T₃ showed a positive association with BP (systolic T₃ = +0.7, P < 0.001 and diastolic R = +3, P = 0.02) and HOMA-IR (R = +1.3, P = 0.009). No significant metabolic associations were found for TSHR-M or TPO antibody positivity. The 14/14 FOXE1–PTL (60% of cohort) was positively associated with free T₃ compared to other genotypes (R = +0.2, P = 0.007) and negatively associated with BP (systolic R = 6, P = 0.006 and diastolic R = 4, P = 0.01).

**Conclusions**

Free T₃ correlated positively with BP and HOMA-IR in this cohort, irrespective of SH aetiology. An unexpected association between FOXE1–PTL polymorphisms and BP was revealed.

**Disclosure**

Society for Endocrinology grant.

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GP.26.04

**Nkx2.5 gene mutations are not associated with congenital heart defects in children with thyroid dysgenesis**

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**Context**

Several specific transcriptional factors, in view of their important role in thyroid organogenesis and thyroid specific gene expression, would be strong candidate genes for the etiology of TD. The homeobox transcription factor Nkx2.5 was thought to be only required for the organogenesis of the heart tube. However, Nkx2.5 embryos also exhibited a smaller outgrowing thyroid bud. Indeed, several loss of function mutations in Nkx2.5 have been described in patients with congenital heart disease (CHD), and an Italian study has identified three mutations in patients with TD.

**Objectives**

To search for genetic alteration in Nkx2.5 gene in patients presenting both TD/CHD and isolated TD.

**Methods**

Among 1051 children screened between 2001 and 2013, 851 children were identified with CH. Individual phenotypes were analyzed in 86 children with TD.

**Results**

Sixty-four (7.4%) of the 86 TD children were identified with CH. Individual phenotypes were analyzed in 86 children with TD. In the 86 TD children with CH, 141 (616 cases) were identified. The mutation screening revealed two known polymorphisms in 48 patients with isolated TD or TD associated with CH. None of them are predicted to result in codon change in conserved domain (p.Glu21; p.Gln181).

**Conclusions**

Nkx2.5 mutations were not found in patients having TD or TD associated with CHD. Nkx2.5 gene might not be a strong candidate gene for mutation screening in population based studies. It would be of interest to attempt to identify additional Nkx2.5 downstream target genes and upstream signaling pathways for a more complete knowledge of the function of this homeobox protein during thyroid migration and morphogenesis.

**Disclosure**

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GP.26.05

**Oral liquid thyroxine assumed at breakfast: preliminary results of the TICO study**

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Many conditions may interfere with intestinal absorption of levothyroxine (L-T4). In addition, it has been demonstrated a failure in the normalisation of TSH values in patients consuming L-T4 tablets with coffee or with water followed by coffee taken shortly afterwards. Recent studies showed that oral liquid L-T4 could remove the problem of L-T4 malabsorption by coffee and food observed with the solid formulations. In addition, it has been demonstrated a failure in the normalisation of TSH values in patients consuming L-T4 tablets with coffee or with water followed by coffee taken shortly afterwards. Recent studies showed that oral liquid L-T4 could remove the problem of L-T4 malabsorption by coffee and food observed with the solid formulations.

**Conclusion**

The TICO study showed that liquid L-T4 can be assumed at breakfast, facilitating compliance to L-T4 replacement therapy. Finally, the oral solution L-T4 could be suitable for patients who cannot swallow the solid formulations.

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GP.26.06

**Analysis of hypothyroidism in patients admitted to internal medicine wards in Spain 2005–2012**

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**Introduction**

Hypothyroidism (hT) is a very common disease that can affect inpatients. We analysed the clinical profile of patients with hT admitted to Internal Medicine using a large clinical-administrative database.

**Methods**

A descriptive analysis based on the minimum-data-set database of the Spanish National Health System of patients who were discharged from the services of Internal Medicine with the diagnoses of hT during 2005–2012 was performed.

**Results**

A total of 3 984 533 patients admitted to Internal Medicine were included, identifying 141 616 cases of hT (3.6%). From the population 75.8% were women, average age in hT patients was 74.34 (s.d.: 14.30), Overall mortality in hT group was 7.6% vs 10% in non hT (pT). The 14.3% of the patients hT were readmitted, whereas in the whole population the 13.3% did it. The average hospital stay was 9.73 (s.d.: 10.04) days. The comorbidities associated to hT were as follows: connective tissue disease (2.2% in hT vs 1.1% in non hT), diabetes mellitus (32.5% vs 27.5% respectively), hypertension (42.1% vs 36.9% respectively), hypercholesterolemia (23.4% vs 16.2% respectively), obesity (12.8% vs 7.5% respectively), anemia (21.9% vs 16.1% respectively), and chronic renal impairment (15.9% vs 11.5% respectively). In the multivariable analysis hT was associated to a lower mortality rate OR 0.71 (95% CI 0.70–0.73; P < 0.05). In the adjusted analysis by age (95% CI 1.052–1.053; P < 0.05) and by comorbidities Charlson index OR 1.246 (95% CI 1.245–1.248; P < 0.05).

**Conclusion**

Hypothyroidism was associated with cardiovascular risk factors as well as other comorbidities (obesity, anemia, kidney failure, and connective tissue pathologies). Some authors suggest that the increase in TSH levels could have a protective effect during admission. However, surprisingly in the hT group there was lower mortality rate. Further studies are needed to confirm this results and determine other involved factors.

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GP.26.07

**Cardiovascular risk factors in autoimmune thyroiditis and subclinical hypothyroidism**

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**Introduction**

Subclinical hypothyroidism appears to be related with an increased risk of cardiovascular disease. It was our objective to evaluate the relationship between autoimmune thyroiditis, subclinical hypothyroidism, and cardiovascular risk factors.

**Methods**

We evaluated thyroid function tests, autoimmune, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, ApoA1, ApoB, Lp(a), homocysteine, high sensitivity CPR, folic acid, vitamin B12, HOMA-IR, HOMA-B, QUICKI.

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Patients with higher levels of total cholesterol (OR = 1.008; P = 0.03), CPR (OR = 1.684; P = 0.04), or anti-thyroglobulin antibodies (OR = 1.002; P = 0.02) have an increased likelihood of having subclinical hypothyroidism. In the total group of patients, we observed positive correlations between TSH and CPR (r = 0.132; P = 0.043), between TSH and HOMA-IR (r = 0.165; P = 0.029), between free T4, and HDL-cholesterol (r = 0.16; P < 0.01), and between free T4 and IGI (r = -0.22; P < 0.01). TSH levels correlated negatively with QUICKI (r = -0.16; P = 0.02), HSI (r = -0.16; P = 0.01), and WBISI (r = -0.16; P = 0.02) and free T4 levels with WBISI (r = -0.18; P < 0.01). In the group with subclinical hypothyroidism, we found negative correlations between free T4 and homocysteine (r = -0.36; P < 0.01) and between free T4 levels and anti-TPO antibodies (r = -0.28; P < 0.02).

Conclusion
The interrelations between thyroid function, lipid profile, CPR, and insulin resistance demonstrate an increase of cardiovascular risk in subclinical hypothyroidism due to autoimmune thyroiditis.

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Prevalence and clinical associations of calcium-sensing receptor and NALP5 autoantibodies in patients with autoimmune polyendocrine syndrome type 1
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Rationale and hypothesis
Autoimmune polyendocrine syndrome type 1 (APS1) is a rare autosomal recessive disease which is characterised by chronic mucocutaneous candidiasis and multiple autoimmune endocrinopathies and results from mutations in the autoimmune regulator (AIRE) gene. Approximately 80% of APS1 patients present with hypoparathyroidism which is suggested to result from aberrant immunoregulatory responses against the parathyroid gland. As patients typically display organ-specific autoantibodies which correlate with a particular clinical manifestation, there has been much research to identify a parathyroid-specific autoantibody target. Previous studies have identified the parathyroid-expressed calcium-sensing receptor (CaSR) and NALP5 as autoantigens in APS1. However, it is unclear if autoantibodies against CaSR or NALP5 are a specific or sensitive marker for APS1-associated hypoparathyroidism.

Methodology
A case–control study including 44 APS1 patients and 38 healthy control subjects. Methods included ELISA, radioligand binding assays, immunoprecipitation assays; DNA sequencing; and statistical analysis. Findings CaSR and NALP5 autoantibodies were detected in 16/44 (36%) and 13/44 (30%) of APS1 patients, respectively, but not in healthy control subjects. No statistically significant association was found between the presence of CaSR or NALP5 autoantibodies and hypoparathyroidism (P > 0.05). The detection of CaSR and NALP5 autoantibodies had specificities of 83 and 50%, and sensitivities of 39 and 26%, respectively, for the diagnosis of hypoparathyroidism. There were no significant associations between the presence of CaSR or NALP5 autoantibodies and either sex, age, or age at disease presentation (P values were > 0.05). However, a significant association between a shorter APS1 duration (< 10 years) and positivity for CaSR autoantibodies was noted (P = 0.019). This was not the case for NALP5 autoantibodies.

Conclusions
Since CaSR and NALP5 autoantibodies are not specific or sensitive markers for hypoparathyroidism in APS1, further investigations are required to identify a useful diagnostic marker for this clinical manifestation in APS1.

Disclosure
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Stepwise logistic regression analysis was performed for testing the importance of amino acid signatures of the binding cleft.

Results and conclusions
We show results for HLA-DR of a big project on the genetics of HT. We found that, indeed, the amino acid signature of the binding cleft, encompassing positions 26, 30, 70, 71, and 74, might be important for the development of the disease, but our results let us also conclude that this model would explain only about 5% of the susceptibility to HT. The results for HLA-DR may also differ when additional genetic and environmental factors are considered simultaneously. It therefore seems reasonable to include this genetic region into analyses encompassing multiple genes as well as non-genetic factors. This will be the next step of our ongoing project.

Disclosure
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Thyroid - hypothyroidism and treatment

**GP.27.01**
The effect of TSH suppression therapy on the cortical bone geometry in the patients with differentiated thyroid cancer

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Background
TSH suppression therapy has been associated with hip and vertebral fracture. However, the relationship between TSH suppression and bone mineral density (BMD) remains controversial. The aim of this study was to evaluate the effect of TSH suppression therapy on cortical bone geometry in differentiated thyroid cancer (DTC) patients.

Methods
This study included 122 subjects (19 men, 27 premenopausal women, and 75 postmenopausal women) who have been on TSH-suppressive doses of levothyroxine after thyroidectomy due to DTC during at least 3 years. Patients were matched with 366 healthy controls. Dual-energy X-ray absorptiometry at the hip and lumbar spine was performed and geometry of hip was analysed.

Results
The mean TSH level was 0.25 ± 0.44 mIU/ml and the proportion of calcium/vitamin D supplement was 51.6% in 122 subjects. TSH suppression therapy did not impair the BMD of patients compared with controls. In addition, cortical bone geometry including cortical width of femur neck (5.5 ± 1.9 vs 5.4 ± 1.1, P = 0.903 in men, 5.9 ± 1.1 vs 5.0 ± 0.6, P = 0.079 in premenopausal women, and 5.0 ± 0.9 vs 5.1 ± 0.7, P = 0.563 in postmenopausal women) and buckling ratio (4.0 ± 2.1 vs 4.0 ± 1.4 in male, 3.0 ± 0.8 vs 3.4 ± 0.3 in premenopausal women, and 3.6 ± 0.7 vs 3.5 ± 0.6 in postmenopausal women) showed no significant difference in patients compared to healthy controls.

Conclusions
There was little evidence of adverse effect of TSH suppression on cortical bone geometry in DTC patients.

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**GP.27.02**
MIVAT vs traditional thyroidecotomy: a 5-year follow up in 284 cases

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Introduction
Minimally invasive video-assisted thyroidectomy (MIVAT) was introduced for the treatment of selected patients. Our experience from 2005 indicates that outcome of surgery in differentiated thyroid cancer (DTC) is comparable in patients treated with MIVAT vs conventional thyroidecotomy; minimally invasive technique is characterized by a better postoperative discomfort.

Material and methods
In this prospective study from July 2005 to December 2009, 284 patients with cytological negative node underwent either MIVAT (n = 102) or conventional thyroidecotomy (n = 182). The following criteria for MIVAT were applied: thyroid volume, nodule size, and pathological criteria. We have collected age, nodule mean size, operative time, serum calcium level pre and post surgery. In follow-up these data were recorded: cumulative dose of radio-active iodine (RAI) and serum thyroglobulin (Tg) at 5 years.

Results
The clinical parameters of the MIVAT and conventional thyroidecotomy groups were comparable except for age (mean 44.8 ± 9.9 years vs 52.3 ± 14.1 years, P = 0.03) and operative time (mean 63 ± 23.5 min vs 54 ± 15.4 min, P = 0.02); the mean tumour size was similar between groups (1.3 ± 0.6 cm vs 1.6 ± 0.8 cm, P = 0.15). Surgical morbidity was similar in both groups. Median follow-up was 5 years. RAI dose (mean 73 ± 36 mCi vs 97 ± 45 mCi, P = 0.33) and serum Tg at 5 years (mean 0.4 ± 0.1 years vs 0.4 ± 0.2 years, P = 0.3) were not significantly different between the minimally invasive and the conventional thyroidecotomy groups.

Conclusion
MIVAT can be safely utilised in patients with DTC providing early oncological outcome comparable to conventional thyroidecotomy. Patients treated with minimally invasive surgery showed an improvement of postoperative pain and cosmetic result.

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**GP.27.03**
Clinical and biochemical factors affecting prognosis of disease persistence in micro papillary thyroid carcinomas

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Introduction
In recent years, micro papillary thyroid carcinomas (mPTCs; ≤ 1.0 cm) are increasingly diagnosed. Although clinical course is usually favourable, disease persistence may occur and multiple treatments needed. We examined factors that could be predictors of clinical behaviour and disease persistence.

Patients and methods
478 mPTC patients (78.9% females) followed-up for 0.6–10 years were classified according to tumour size in group 1: 0.1–0.2 (n = 85), group 2: 0.3–0.4 (n = 81), group 3: 0.5–0.6 (n = 96), group 4: 0.7–0.8 (n = 79), and group 5: 0.9–1.0 cm (n = 137).

Results
Median age at diagnosis, sex and histological type did not differ between subgroups. Capsular and lymph node invasion as well as soft tissue involvement was more frequent with increasing tumor size (P < 0.001). Multifocality and distant metastasis at diagnosis was similar. Patients with mPTCs ≥ 0.7 cm (groups 4 and 5) underwent more frequently lymph node dissection (P = 0.009) as well as ablation with 131I (P < 0.001). In those who underwent thyroid ablation, disease remission during the 12-month Tg-stimulation (Tg ≤ 1.0 ng/ml) was less frequent in group 5 (group 1: 85.7%, group 2: 88.2%, group 3: 92.7%, group 4: 85.4%, and group 5: 69.1%, P = 0.007). However, after multiple treatments (> 1 surgeries and/or repeated 131I administration) the disease outcome did not differ significantly. The 10-year probability of lack of progression of disease did not differ between groups (100% vs 97% vs 100%, vs 100%, vs 95.5%, respectively, P = 0.3). In Cox proportional hazard analysis when age at diagnosis, tumour size, lymph node, capsular and tissue invasion were taken into account the only predictor for disease progression was lymph node invasion (HR 1.1, 95% CI 0.004–0.379, P = 0.005). Similar results were found when only those who underwent ablation with 131I were examined. 10.3% of patients with lymph node invasion showed disease progression; all belonged to group 5 (P = 0.038, Pearson χ2).

Conclusions
Although, patients with tumours ≥ 0.9 cm have more frequently disease persistence, the final outcome is similar in all mPTC groups. Lymph node invasion may be the only factor predicting disease progression in mPTCs.

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GP.27.04
TIM16 inhibition enhances sensitivity to paclitaxel and decreases calcitonin secretion by reducing mitochondrial membrane potential in a human medullary thyroid carcinoma cell line
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TIM16, a protein of the translocone complex TIM23 of the mitochondrial inner membrane, is encoded by the Magnas gene. Magnas silencing has been associated with a greater sensitivity to apoptotic stimuli in pituitary adenoma cell lines. We recently demonstrated that in a human medullary thyroid carcinoma cell line (TT) compound 5, a TIM16 inhibitor, was not cytotoxic but enhanced the proapoptotic effects of staurosporine. The aim of our study is to verify whether mitochondrial function is involved in compound 5 effects. To evaluate cell viability we performed ATPlase assay, while caspase 3/7 assay was used to determine apoptotic activation. ELISA test was used for calcitonin detection in cell culture medium, while TMRM assay was employed to evaluate mitochondrial membrane potential (MMP). Our data show that paclitaxel 10 nM was reduced cell viability by 40%, while compound 5 alone had no effects. However, compound 5 was able to significantly increase the effects of paclitaxel by nearly 14%. In addition, paclitaxel increased caspase 3/7 activity by 130%, which was further increased by co-incubation with compound 5. In addition, we found that compound 5 was able to reduce basal and pentagastrin induced calcitonin secretion. Furthermore, compound 5 and paclitaxel decreased MMP (by ~15 and ~20% vs CT respectively), and their combination was even more potente (~50% vs CT). In conclusion, compound 5 could represent a tool to increase the effects of chemotherapeutic agents and to control hypercalcitoninemia in medullary thyroid carcinoma.

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GP.27.05
Effect of a very low dose of rituximab on active moderate-severe Graves’ orbitopathy: an interim report
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Previous studies have shown that Rituximab (RTX) is effective as a disease modifying drug at doses of 500 mg or 1000×2 mg in active Graves’ orbitopathy (GO). We have conducted a pilot study (EUDRACT 2012-001980-53) in which patients with active moderate-severe GO were treated with a single infusion of low dose RTX (100 mg). Ten patients were enrolled of whom seven completed the study at 52 weeks. Five patients did not respond to a previous treatment with i.v. methylprednisolone, whereas five had newly diagnosed GO. Disease activity was assessed with the clinical activity score (CAS) and severity with NOSPECS score. The primary endpoint was the decrease of the CAS of 2 points or CAS ≤3.

Results
Of the seven patients who completed the study, six had inactive disease at 12 weeks (ANOVA, P = 0.01); one was submitted to surgical orbital decompression because of signs of optic neuropathy (ON). Another patient, although who had disease inactivation at 12 weeks, underwent surgical orbital decompression at 22 weeks because of suspected subclinical ON. At 24 weeks four patients were inactive (ANOVA, P = 0.001); one had a transient disease reactivation with stabilization at 40 weeks. The treatment was well tolerated with only minor infusion-related reactions.

Conclusion
Very low dose of RTX seems effective in disease inactivation but may not modify the natural course of disease as has been observed with higher therapeutic doses.

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GP.27.06
hCG levels are essential for the correct interpretation of gestational TSH levels: the clinical risk assessment of premature delivery
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Context
High maternal TSH and/or low FT4 during pregnancy is associated with an increased risk of premature delivery. hCG is the main determinant of thyroid function changes during pregnancy but has a versatile pattern with high inter and intra-individual variability. We hypothesised that the correct interpretation of thyroid function tests and its use in the risk assessment of premature delivery during pregnancy depend on hCG levels.

Design, setting, and participants
TSH, FT4, hCG, and TPO-antibody levels were available in 5956 women. In logistic regression models for premature delivery we tested for interaction between TSH or FT4 and hCG and when significant analyses were stratified. All analyses were adjusted for maternal age, smoking, education level, ethnicity, parity, BMI, height, and foetal gender.

Results
The association between TSH levels and premature delivery was different according to hCG levels (P interaction = 0.02). The risk of premature delivery in women with high TSH levels \( \geq 85\% \), \( \geq 90\% \), or \( \geq 95\% \) was increased two-, three-, and six-fold respectively \((P = 0.001)\). The association between FT4 levels and premature delivery was not different according to hCG levels (P interaction = 0.23). However, women with very low FT4 levels \((\leq 3\text{rd percentile})\) had different risks for premature delivery according to hCG (low to high): OR 1.99–3.11; \( P = 0.02 \). All results remained similar after exclusion of TPOAb positive women, women with preeclampsia or amongst women with spontaneous premature delivery only.

Conclusion
The addition of hCG may improve the risk assessment of premature delivery according to TSH. High TSH levels despite high hCG levels reflect the inability of thyroid function to increase according to hCG stimulation. This inability to increase is a novel risk factor for premature delivery. Future studies are needed to replicate these results and incorporate these findings into clinical decision models.

Disclosure
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GP.27.07
Plasmapheresis in thyroid storm caused by exogenous thyroid hormone intake: a case series
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Thyroid storm (TS) is one extreme of a continuum beginning with thyrotoxicosis. It’s rarely caused by exogenous thyroid hormone intake (ETHI). Aggressive medical therapy is the cornerstone of treatment; nevertheless, it might not be sufficient. Plasmapheresis is an extracorporeal technique that can rapidly lower thyroid hormone levels. The aim of this study was to assess the efficacy of plasmapheresis in TS secondary to ETHI. We evaluated retrospectively all TS cases (Burch–Wartofsky score > 45) caused by ETHI, treated with plasmapheresis between 1991 and 2014 in a tertiary hospital. Patient clinical data, normal thyroglobulin and negative anti-thyroglobulin antibodies ruled out endogenous causes. Statistical analysis was performed with Wilcoxon’s test (SPSS v.21).

Five cases were recorded. The median age was 45 years and four patients were female. The Burch–Wartofsky score ranged from 50 to 85. All patients presented with delirium, the median heart rate was 134 b.p.m. and four patients required an ICU admission. Plasmapheresis sessions ranged from 3 to 4 and were started between days 2 and 5 after admission. Before the first plasmapheresis, median TT4 was 70 μg/dl (4.5–12.5), FT4 17.2 ng/dl (0.8–1.5), TT3 1800 ng/dl (80–200), and FT3 46 μg/ml (1.5–5). The first session induced a significant decrease in median TT4 and FT4 levels of 40 and 46% respectively \((P = 0.004)\). After the last session, a significant large decrease in all thyroid hormone levels was observed: TT4 – 75%, FT4 – 72%, TT3 – 92%, and FT3 – 85%. \( Z = -2.023, P = 0.043, r = 0.64 \). Euthyroidism was achieved after a median of 12 days.
Graves’ orbitopathy (GO) is a common complication of Graves’ disease (GD) which is often responding poorly to therapy. GO may develop before or together with, or during the course of GD. In an individual patient, the development of GO cannot be predicted. We assumed that orbital autoimmune activity is predictable using orbital 99mTc-labelled diethylenetriamine pentaacetic acid (99mTc-DTPA) SPECT. We aimed to determine whether any orbital autoimmune activity can be identified in patients who do not develop GO during their follow-up. Fifty-four orbits of 27 patients newly diagnosed with GD were entered into the study. Patients with present GO were excluded. None of the patients had received antithyroid drugs or ophthalmic measures before entering the study. An initial 99mTc-DTPA SPECT was performed and DTPA uptake as sign of disease signs of GO occurred, and a final SPECT was performed at the end of the follow-up period, after 1 year. Twenty orbits of control patients who underwent DTPA SPECT of the hands for Raynaud’s phenomenon served as controls. During the 2-year follow-up, six out of the 27 patients (22%) were diagnosed with newly developed GO. The mean initial DTPA uptake of the orbits of GD patients with or without later developing GO was significantly higher than results obtained from the control group (10.45 ± 1.72, 9.18 ± 1.18, and 7.7 ± 2.44 MBq/cm², respectively, P < 0.05). Initial DTPA uptake values of the six patients who later developed GO were not different from the rest of the GD group. All GD patients have mild orbital activity signs by the DTPA technique in the early stage of GD, irrespective of development or lack of GO during the course of GD. This uniform ongoing subclinical inflammation may be a reversible early stage of GO.

Patients and methods
Retrospective analysis of data from patients with ECS from NETs collected in 14 centres between 1986 and 2014, obtained by a specific questionnaire.

Results
96 patients, 58.3% females, mean (s.d.) age at diagnosis 50.4 ± 15 years. Clinical presentation included hypertension (87%), diabetes mellitus (67%), proximal myopathy (67%), weight loss (28%), skin fragility (53%), hypercoagulopathy (28%), osteoporosis (47%), and psychiatric disease (32%). Regarding prevalence of NETs, 42.7% were bronchial carcinoids, 3.1% small-cell lung carcinoma (SCLC), 13.5% pancreatic (p), 8.3% thymic, 4.2% phaeochromocytoma, 5.2% others, and 23% occult. Tumour diameter of p-NETs was larger than that of bronchial carcinoids (47.3 ± 34 mm vs. 28 ± 21.4 mm, P = 0.035). Distant metastases were more prevalent in p-NETs, SCLC and thymic than in bronchial carcinoids and occult (77.7, 66.7, 50% vs. 24.4, 15.6% respectively). Among 45 NETs with available Ki67, 46.7% were G1, 37.8% G2 and 15.6% G3. Immunostaining for ACTH was positive in 85.4%. Surgery was performed in 54.1%, steroidogenesis inhibitors in 77.1%, somatostatin analogues in 53.1%, cabergoline in 44%, mifepristone in 1%, everolimus in 6.2%, sunfortin in 1%, chemotherapy in 23%, PRRT in 10.4%, mono/bilateral adrenalectomy in 29%, and interventional treatments of liver metastases in 5.2%. Mean survival was 78 months (range 1–276), 24% died due to NET.

Conclusions
Bronchial carcinoids are the main NET associated with ECS, whereas 23% of cases are still occult, p-NETs are larger than bronchial carcinoids and more aggressive. Hystopathology, grading and distant metastases are the main prognostic factors. A multimodal treatment, including surgery of NET whenever possible, and adrenalectomy to definitively solve hypercortisolism thus reducing the risk of complications, can prolong survival.

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Surgery is the only effective therapy for insulinoma patients, therefore there is a necessity to develop diagnostic strategies in cases of unknown tumour location, possibly through the use of new biomarkers. 99mTc labelled glucagon-like peptide 1 analogue (99mTc-GLP1) scintigraphy has been developed in our centre as an imaging technique of insulinoma. Labelled GLP1 analogue might also be applied in diagnosis of various forms of neuroendocrine tumours allowing to determine the range of surgery in its focal and diffuse types, if suitable.

Material and methods

Study included: 40 patients with suspected insulinoma in whom CT/MR/UES/SRS failed to visualise tumour thus excluding surgical intervention, 3 patients with malignant insulinoma and three with neuroendocrine tumours (to assess its type form). Lys(40)(Ahx-HYNIC-99mTc/EDDA)NH2 exendin-4-SPECT/CT with volumetric analysis was performed.

Results

21/40 cases were true positive with focal tracer uptake in pancreas including histopathologically confirmed bizonal insulinoma. In all operated patients symptoms resolved postoperatively. One false negative result appeared to be malignant insulinoma, in one no tumour was found (false positive result). Nine cases were true negative with no 99mTc-GLP1 uptake (reactive hypoglycemia or Munchausen syndrome); eight patients were lost from follow up. Sensitivity, specificity, PPV of 99mTc-GLP1-SPECT/CT were 95%, 90%, and 95% respectively. Scintigraphy revealed diffuse tracer uptake in two, and a focal lesion in one neuroendocrine metastasis (histopathology: coexistent nesidioblastosis and insulinoma). 99mTc-GLP1–SPECT/CT confirmed different biology of primary tumour (PT) and metastases in malignant insulinoma (phenomenon well known in NENs): both PT and metastases were negative in one patient, PT positive and metastases negative in 1, PT negative and metastases positive in last case.

Conclusions

In our study 99mTc-GLP1–SPECT/CT proved to be helpful in management of persistent hypoglycaemia patients. 99mTc-GLP1–SPECT/CT could also be considered in the former stages of diagnostic schemes to optimise the procedures with a more effective strategy to allow sparing operation as well as to improve the quality of life of these patients.

Disclosure

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GP.28.04

Receptor tyrosine kinase expression and their role in the response to target therapy in bronchopulmonary NET

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Surgery is not feasible for infiltrating and metastatic bronchopulmonary NET (BP-NET). In those cases, medical therapy is tried with controversial results. Thus, it is important to identify new therapeutic targets to provide adequate medical treatment for patients with BP-NET. Sunitinib, is a multi-targeted receptor tyrosine kinase inhibitor (TKI), mainly described to inhibit VEGFR. The aim of our study is to verify whether insulin receptor (IR), IGF1R, and EGFPR could be involved in Sunitinib mechanism of action in BP-NET cells.

For this purpose human BP-NET cell lines and human BP-NET primary cultures were treated with Sunitinib and/or EGF, IGF1, or VEGF. Cell viability and caspase 3/7 activation were measured after 48 h of treatment. Receptor expression was detected by Western blot in both cell lines and primary cultures. Phosphorylation of IGF1R and EGFR was analysed by Alphascreen sure fire assay.

Our results show that Sunitinib is capable of inhibiting cell viability of BP-NET cell lines and primary cultures, and activates caspase 3/7. Both events are counteracted by EGF and IGF1, but not by VEGF. Moreover, both cell lines and tissues invariably express IR, IGF1, and EGFR, while VEGFRs are expressed only in some samples. Treatment with Sunitinib decreased the phosphorylation of both EGFR and IGF1, in both cell lines and primary cultures.

In conclusion, these data indicate that the expression of EGFR and IGF1R are important for Sunitinib action in BP-NET. The effects of Sunitinib on BP-NET cell viability could be due to a double inhibition of EGFR and IGF1R, while the role of IR needs to be further investigated.

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GP.28.05

Filamin-A is involved in stabilisation, signal transduction, and angiogenesis regulation mediated by somatostatin receptor 2 in pancreatic neuroendocrine tumors

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Somatostatin receptor type 2 (SST2) is the main pharmacological target of long-acting somatostatin analogues (SSA) widely used in patients with pancreatic neuroendocrine tumours (P-NETs). A subset of patients is resistant to SSA, although the molecular mechanisms responsible for resistance are poorly understood. Several studies identified cytoskeleton protein interactions as determinant in receptor anchoring, expression and signalling. Since SST2 was recently demonstrated to associate to filamin A (FLNA), we investigated the role of FLNA on SST2 signalling, we analysed cyclin D1 expression, ERK1/2 phosphorylation in FLNA-silenced QGP1 cells. Similarly, BIM23120 inhibited forskolin-stimulated cAMP accumulation in cells transfected with negative control and this effect was abrogated in FLNA silenced cells. In addition, BIM23120 incubation induced a decrease in both VEGF expression (−31±7% in negative control transfected cells, P<0.001 vs untreated cells) and VEGF release into control cell supernatants (−39±24%, P<0.05 vs untreated cells) and these effects being completely abolished by FLNA silencing. In conclusion, these results demonstrate that FLNA is required for SST2 signalling, stabilisation and angiogenesis in tumoral pancreatic neuroendocrine cells, thus suggesting a possible role of this cytoskeleton protein in determining the different responsiveness to SSA observed in P-NET patients.

Disclosure

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**GP.28.06**

Patient-reported time to diagnosis of neuroendocrine tumors (NETs) in Europe: results from the first global NET patient survey: a collaboration between the International Neuroendocrine Cancer Alliance (INCA) and Novartis

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Background

Neuroendocrine tumor (NET) symptoms are often similar to common conditions or may not arise until metastasis occurs, delaying diagnosis and impacting survival. We present data on time to diagnosis from the European (EU) NET patient perspective.

Methods

In 2014, 1928 NET patients from >12 countries (Europe (n = 763): Belgium, Bulgaria, France, Germany, Norway, UK, and other EU countries (not specified); Americas; Asia; Oceania) participated in a survey on the NET patient experience, including diagnosis, conducted by Hall and Partners on behalf of International Neuroendocrine Cancer Alliance (INCA)/Novartis and funded by Novartis. All comparisons were significant at \( P < 0.05 \).

Results

60% of respondents reported being diagnosed <5 years ago; median time from symptom onset to diagnosis was 24 months (for overall population and patients diagnosed <5 vs ≥5 years ago). Notably, 24% reported a ≥5-year lag for diagnosis. 63% had metastases at diagnosis (higher in patients diagnosed <5 years (67%) vs ≥5 years (57%) ago). Patients saw a mean of seven health care providers (HCPs) with a mean of 4.7 HCP visits/year, only 25% were diagnosed there. For 43% of patients, NET was not the initial diagnosis, and 26% were diagnosed with NETs during testing for another condition. The most common early diagnoses were digestive disorders. Most patients (74%) did not suspect their symptoms were cancer related. Patients diagnosed <5 years ago felt more informed (able to get answers (65%) had sufficient information (58%)) than those diagnosed ≥5 years ago (56%/48% respectively). The majority (65%) felt there was much room for improvement in NET diagnosis: 52% wanted clearer information about long-term impact; 42% wanted better direction regarding NET-related information.

Conclusion

This large European NET patient survey demonstrated delays in NET diagnosis in EU patients, consistent with global findings in the literature, and identified areas for improvement.

Disclosure

The Global NET Patient Survey was conducted as a collaboration between the INCA and Novartis Pharmaceuticals. Funding for this survey was provided by Novartis.

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**GP.28.07**

Complete remission of hepatic metastasis after total gastrectomy for a gastric carcinoid tumor type 1: a case report

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Gastric carcinoids secondary to autoimmune atrophic gastritis (GC type 1) are usually well differentiated neoplasia, with an indolent course and an excellent overall prognosis. However, a subset of these tumors (<5%) may develop advanced disease, with lymph node and/or hepatic metastasis. The pathogenesis of these carcinoids is related to chronic trophic stimuli to enterochromaffin-like (ECL) cells due to chronic hypergastrinemia. Treatments directed to remove the source of hypergastrinemia (such as antrectomy and SSAs) have been used with good results in localized tumors. These approaches had been used in localized disease, while its effectiveness had never been demonstrated in metastatic cases. In this report, we describe the case of a woman with type 1 gastric carcinoid with liver metastasis documented by abdominal CT and 68Ga-PET DOTATOC. The patient underwent total gastrectomy with lymph node dissection; during surgery an hepatic US was performed, showing seven subcentimeter metastases. Histological examination revealed a neuroendocrine neoplasm G2 (WHO 2010) of 30 mm. Ki67 20%, 15 mitoses/10 HPF; chronic gastritis and micromass hyperplasia of endocrine cells was associated. During the early months of follow up a gradual reduction in size of liver metastases, until the complete disappearance of them was observed. This is to our knowledge the first case ever described in literature of complete remission of liver metastatic type 1 GC after removal of the source of excessive gastrin, showing a possible preservation of responsiveness of metastases to gastrinemic stimuli. This could lead to a possible change in therapeutic approach in these neoplasms.

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**GP.28.08**

General characteristics and evaluation of β-cell function and insulin sensitivity in a large monocentric series of insulinomas

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Background

Insulinomas are the most common functional neuroendocrine tumours of the pancreas. Hypoglycaemic manifestations are highly variable and largely independent on tumour size and severity of insulin hypersecretion.

Objectives

In this study we investigated the clinical, biological and tumoural characteristics of a large series of patients with insulinoma and we evaluated the sensitivity of peripheral tissues to insulin before and after surgery.

Patients and methods

This is a retrospective analysis of 40 patients followed between 1982 and 2012 in our academic hospital. Insulin sensitivity and β-cell function could be evaluated by HOMA test in a subset of these patients.

Results

The mean age at onset of symptoms was 48.8 ± 20.1 years and the mean age at diagnosis was 50.7 ± 19.9 years. A sex ratio of 0.6 (15 men for 25 women) was found. Adrenergic symptoms were observed in 75% of patients and neuroglucopenic symptoms in 90%. In addition, 33% of patients suffered from epileptic disorders and 20% from psychiatric manifestations. Weight gain was observed in 40% of the patients. The most effective imaging techniques to localize the tumour were endoscopic ultrasound (90% sensitivity) and intraoperative ultrasound (94% sensitivity). Insulin sensitivity (measured outside hypoglycaemic episodes) was greatly reduced in patients with insulinoma (38.9 ± 22.3%), while β-cell function was increased (359.0 ± 171.5%), but to a variable extent (range 110.6–678.6%). After complete resection of the tumour and disappearance of hypoglycaemia, insulin sensitivity normalizes from 36.9 ± 19.0 to 80.6 ± 18.4% (P < 0.001) in 12 cured patients with available pre- and post-operative HOMA tests.

Conclusion

The general characteristics of our series are consistent with the general features reported for insulinomas in the literature. We also show that in response to chronic hyperinsulinemia, patients with insulinoma develop protective mechanisms responsible for a marked insulin resistance, which is fully reversible after complete resection of the tumour.

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**GP.28.09**

Association of angiopoietin/TIE2 plasma level and VEGF system with progression in gastroenteropancreatic neuroendocrine tumors

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Introduction

Angiopoietins (ANG)-1 and 2, their receptor TIE2, and the vascular endothelial growth factor (VEGF) are involved in the process of angiogenesis. However, their...
role in the pathogenesis and development of gastroenteropancreatic neuroendo- 
crine tumours (GEP-NETs) is not completely understood. In a previous study of 
42 patients with GEP-NET, we observed an elevation of these serum markers, 
especially in those with metastatic disease. The objective of this study was to 
 analyse the relationship between plasma levels of the ANG/TIE2-VEGF system in patients with GEP-NETs who exhibited progression after 3 years of follow-up. 

Methods and materials 
26 Patients with GEP-NETs were studied. Primary location of tumours was 
pancreas (n = 13) and intestine (n = 13). Plasma levels of ANG-1, ANG-2, TIE2 
and VEGF were determined by ELISA. We evaluated response to medical and/or 
surgical treatment using clinical and radiological criteria and patients were 
assigned to three categories (complete remission, stable disease or progressive 
response), accordingly. Statistical nonparametric analysis tests was performed. 

Results 
At diagnosis, 13 patients had positive regional lymph nodes and 13 distant 
metastases. Thirteen patients achieved complete response, six had stabilization 
and seven were classified as disease progression. Plasma TIE2 levels at initial 
evaluation were higher in patients who had progressive disease (31 803.17 ± 
5495.55 pg/ml) vs those who had complete response (18 930.00 ± 3914.20 pg/ml) 
 or remained stable (25 236.67 ± 1072.40 pg/ml) (P = 0.014). No differences were 
found in these angiogenic markers when comparing primary tumour location 
(pancreas or intestine), the presence or absence of metastases, or response to 
therapy, accordingly. Statistical nonparametric analysis tests was performed. 

Conclusion 
The2 plasma values are higher in patients with GEP-NETs with progressive 
disease. This suggests a possible involvement of ANG/TIE2 system in the 
pathogenesis of GEP-NETs and a possible relevance as diagnostic and/or 
therapeutic target.

Endocrine tumours and neoplasia - Adrenal Tumour 

Mitotane inhibits sterol-o-acyltransferase leading to lipid-mediated 
endoplasmic reticulum stress and apoptosis of adrenocortical 
carcinoma cells 
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Context 
Mitotane is the only drug approved for treatment of adrenocortical carcinoma 
(ACC) and in clinical use for more than 50 years. Mitotane counteracts both 
tumour growth and tumoral steroid hormone production but treatment is 
associated with severe side effects. The molecular mechanism of mitotane is 
still unknown, which hampers progress in treatment of ACC.

Objective 
To identify the mechanism of action and molecular target of mitotane.

Methods 
We combined expression genomics, proteomics and lipidomics in an in vitro 
study using the NCI-H295 ACC reference cell line and four non-steroidogenic 
cell lines. 

Results 
Pathway analysis of gene expression data demonstrated activation of endoplasmic 
reticulum (ER) stress and altered lipid metabolism. Strongly increased expression of 
ER-stress marker C/EBP-homologous protein (CHOP, 26.7 ± 0.1-fold, 
P < 0.001) and activated XBP1-mRNA splicing (23.2 ± 3.2-fold, P < 0.001) was 
found in sharp contrast to weak ER-stress activation in non-steroidogenic cell lines 
(HepG2: 2.61 ± 0.4-fold, HEK293: 2.5/3.7, HeLa: 3.56/4.3, IMR-32: 1.5/2.1). 
ER-stress experimentally triggered by thapsigargin mimicked mitotane effects 
on steroidogenesis and apoptosis. Mass spectrometry revealed specific mitotane- 
induced lipid alterations with elevated free cholesterol (2.53-fold, 
P < 0.05), oxysterols like 7-dehydrocholesterol (5.4-fold, 
P < 0.001) and fatty acids, e.g. 
C20:4 (arachidonic acid: 3.2-fold, 
P < 0.001) in NCI-H295 cells but not in other cell lines. Inhibition of Acyl-CoA-Cholesterol-Acyl-transferase (SOAT1) by 
mitotane (IC50 = 22 μM) was identified as the mechanism underlying these 
events. 

Conclusions 
Mitotane confers adrenal specific cytotoxicity and down-regulation of steroido- 
genesis by lipid-induced ER-stress through inhibition of SOAT-activity. This 
finding opens new avenues for improved ACC treatment. Cancer specific lipid 
metabolism may be a treatment target in other types of cancer. 

Disclosure 
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GP 29.02

Investigation of a novel liposomal chemotherapy protocol in three 
preclinical models for adrenocortical carcinoma in vivo 
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Recently, we demonstrated for adrenocortical carcinoma (ACC) promising 
antimutual effects for LEDP-M (etoposide, liposomal doxorubicin, 
liposomal cisplatin, mitotane) a novel liposomal variant of the classical 
EDP-M protocol (etoposide, doxorubicin, cisplatin, mitotane). However, 
clinical translation of novel therapeutic regimens remains challenging due 
to high tumor heterogeneity. Thus, to obtain preclinical results with more 
clinically predictive power we investigated for the first time LEDP-M in 
three different xenograft models for ACC in vivo. Moreover, we included 
liposomal etoposide resulting in a novel treatment scheme called L(l)EDP- 
M. After one therapeutic cycle NCI-H295R, SW-13 and SJ-ACC3 tumours were 
excised and immuno-histochemically (cells/high power fields (HPF)) 
analysed regarding total number of tumor cells (K67 positive and 
negative/HPF) and apoptosis (TUNEL positive cells/HPF). In previous 
experiments on NCI-H295R xenografts we detected a significant reduction in 
overall tumor cell count for LEDP-M which was in the current study not 
reached by L(l)EDP-M. In contrast, regarding apoptosis L(l)EDP-M 
(P < 0.01) led to a further improvement of therapeutic efficacy as compared 
with LEDP-M (P < 0.05 vs controls). In SW-13 xenografts, the number of 
tumor cells decreased in all treatment schemes with highest therapeutic 
efficacy of the liposomal variants (EDP-M: 20.5 
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17th European Congress of Endocrinology 2015
GP.29.03
ImmunoeXpressions of CYP11B2 and HSD3B2 in genetically characterised aldosterone producing adenomas
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Primary aldosteronism caused by aldosterone-producing adenoma (APA) or bilateral adrenal hyperplasia is the most prevalent cause of secondary hypertension. Somatic mutations of KCNJ5, ATP1A1, CACNA1D and ATP2B2 have been shown to be involved in the formation of APA. We studied the immunoeXpressions of CYP11B2 and HSD3B2, the rate-limiting enzyme for aldosterone production and the prevalent isoform of β-HSD found in APA respectively, and correlated these findings with the mutation status, histopathology of APA and to the biochemical and clinical outcome of adrenalectomy. In our study, APA tissues obtained by adrenalectomy were divided into five subgroups (KCNJ5, ATP1A1, CACNA1D, ATP2B2 or WT) after characterization of the respective mutational status by direct or exome sequencing. Paraffin-embedded tumors were evaluated for size and cell composition, Immunolocalization and semi-quantitative immunoeXpressions of CYP11B2 and HSD3B2 were analysed. Scoring staining intensity was determined along with clinical findings. Our results show that a majority of APAs consists of both zona fasciculata-like and zona glomerulosa (ZG)-like cells. CACNA1D mutated-APA were significantly smaller than KCNJ5 mutated-APA (P < 0.05). All mutated APAs presented CYP11B2 positive clusters or variably stained scattered cells while WT APAs were weakly or negatively stained for CYP11B2 with only clusters in adjacent ZG. H-Score for CYP11B2 was significantly different between WT and KCNJ5 mutated APAs (P < 0.05). Immunoreactivity of HSD3B2 was strongly present in all analyzed tissues independently of the tumoural cell type and no significant difference was noted between the subgroups. HSD3B2 H-scores. Biochemically, serum potassium levels of all patients were normalized after adrenalectomy. High aldosterone to renin ratio at diagnosis and shorter duration of hypertension preceding surgery were associated with better clinical outcome. Our findings suggest that KCNJ5 and not ATP1A1, CACNA1D or ATP2B2 mutated APAs have significantly different CYP11B2 immunoreactivity, compared with WT-APA while immunoreactivities of HSD3B2 or CYP11B2 are not correlated with outcome.

Disclosure
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GP.29.04
Synergistic action of 9-cis retinoic acid and mitotane in a H295R adrenocortical cancer xenograft model
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Background
Current drug treatment options for adrenocortical carcinoma (ACC) are rather limited and intensive efforts are going on to find novel effective agents. In our previous functional genomics study, retinoid signalling via the retinoid X receptor (RXR) was identified as a major pathogenic pathway in ACC and we have demonstrated the in vitro activity of 9-cis retinoic acid (9-cisRA) acting via the RXR on NCI-H295R cells and also found that 9-cisRA has antitumour effects in a small pilot xenograft study.

Aim
To investigate the antitumour effect of 9-cisRA and its combination with mitotane in a large-scale xenograft study.

Methods
43 male SCID mice xenografted with NCI-H295R cells were treated in four groups (i) control – corn oil vehicle, ii) 5 mg/kg 9-cisRA, iii) 200 mg/kg mitotane, iv) 5 mg/kg 9-cisRA + 200 mg/kg mitotane) for 28 days. Tumor size follow-up, histological and immunohistochemical (Ki-67) analysis, tissue gene expression microarray (4X44 K Agilent Whole Genome Microarray) have been performed. Quantitative real-time-PCR (TaqMan) was used for the validation of the microarray results and to detect circulating microRNAs.

Results
Both 9-cisRA and mitotane reduced tumor growth relative to control, but only the combination of the two agents resulted in significant tumour size reduction. The Ki-67 index was significantly reduced in both 9-cisRA and 9-cisRA+mitotane groups. Gene expression analysis revealed 483 genes with significant differences in expression, but only without Benjamini-Hochberg correction. Seven genes have been selected for validation by qRT-PCR, but only one (APOA4) was found significantly increased in the combined group compared with the control. The expression of circulating hsa-mir-483-5p was found significantly reduced in combined treatment relative to control.

Conclusions
Our results show that 9-cisRA might be a helpful additive in the treatment of ACC in combination with mitotane, but its mechanism of action awaits further investigations.

Disclosure
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GP.29.05
EGFR as potential new molecular target in the medical treatment of adrenocortical cancer
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Adrenocortical cancer (ACC) is a rare and aggressive malignancy. Currently the main therapeutic option is surgery, but due to difficult and delayed diagnosis and to the onset of metastases, medical therapy is often tried. ACC treatment is mainly represented by Mitotane alone or in association with chemotherapy, with variable results. Understanding the molecular mechanisms that regulate ACC proliferation could be useful to identify new therapeutic options. Sunitinib, a multitarget tyrosine-kinase inhibitor, showed controversial results in phase II trials for advanced refractory ACC. It has been previously demonstrated that epidermal growth factor (EGF) increases HSD3B2 expression in ACC cells. The aim of our study is to verify whether EGF pathway could represent a target for Sunitinib in human ACC cells. For this purpose we tested two human adrenocortical carcinoma cell lines (SW13 and NCI-H295 cells) and human adrenal tumor primary cultures. We found that EGF increased proliferation and reduced apoptosis not only in SW13 but also in adrenal tumour primary culture, while it did not affect NCI-H295 cells. Sunitinib reduced cell viability in both cell lines, being counteracted by EGF in SW13 cells and in the majority of primary cultures analysed. We investigated in both cell lines the expression of EGFR family members, which are more expressed in SW13 cells as compared to NCI-H295 cells. Moreover, we investigated the intracellular signal transduction pathway of EGF in ACC cells. Our results show that in SW13 cells Sunitinib inhibited EGF phosphorylation on tyrosine 1068, and counteracted EGF-induced phosphorylation of ERK1/2. In SW13 Sunitinib increased the expression of SAPK/JNK leading to caspase 3/7 activation. In NCI-H295 Sunitinib did not reduce EGF phosphorylation, but inhibits PI3K/mTOR/AKT pathway. To verify the involvement of EGF in regulating ACC cell viability we tested Erlotinib, a selective EGFR inhibitor, in the two cell lines. We found that Erlotinib was capable of dose dependently reducing cell viability and activating caspase 3/7 in SW13 cell line, having no effects on NCI-H295 cells. Therefore, EGFR may be important in regulating EGF expressing ACC cell proliferation. In conclusion, our data suggest that EGF pathway could represent a new molecular target in drug design for treatment of ACC that display enhanced EGFR expression.

Disclosure
None.

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**GP.29.06**

The incidence of consecutive manifestations of VHL disease

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Background

Von Hippel Lindau (VHL) disease is a rare tumour syndrome with a high penetrance. VHL mutation carriers develop numerous disease related manifestations in multiple organs during life, but precise difference in growth velocity and incidence of lesions in different organs is still unknown. We aimed to gain insight in the incidence of consecutive new disease manifestations in the organs of patients with VHL.

Patients and methods

Clinical data including age at diagnosis of each new VHL-related manifestation of 75 VHL mutation carriers, with standardised follow-up, in two Dutch VHL-expert centres were retrospectively evaluated. Only consecutive lesions in the retinoblastoma, the CNS, the kidneys and the pancreas were analysed. New organ lesions were defined as a new organ manifestations detected on imaging or in case of retinal lesions detected by fundoscopy. The Kaplan Meier method was used to construct the cumulative proportions of first and all consecutive manifestations in each organ against age. The cumulative average number of manifestations in all organs during life was calculated by summing these cumulative proportions. Poisson model parameters served to calculate average time to the detection of VHL manifestations in each organ.

Results

Consecutive VHL-related kidney and retina manifestations during life occur according to Poisson distribution model. The second VHL pancreas manifestation occurred later and the consecutive CNS hemangioblastomas were detected earlier than predicted by the Poisson model. The average total systemic number of manifestations rises in a linear way to seven VHL-related manifestations at age 60 years.

Conclusion

The incidence of new VHL-related manifestations after the first organ involvement is highly constant during life in VHL-carriers. Therefore, the accelerations and arrests in appearance of new manifestations observed in individual subjects are caused by the randomness of events and not by variation in disease activity.

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**GP.29.07**

Penetration and optimal surveillance for SDHB mutation carriers

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Context

Germline mutations of the gene encoding succinate dehydrogenase subunit B (SDHB) predispose to head and neck paraganglioma (HNPG), sympathetic PGL, phaeochromocytoma and renal cell carcinoma for which regular surveillance is required. SDHB-associated tumors harbor germline and somatic mutations, consistent with Knudson’s two-hit hypothesis stating that the combination of an inactivating germline mutation as a first hit and somatic loss of function of the wild type allele as a second hit is essential for tumor development. The aim of this study was to assess the penetrance and optimal surveillance for different manifestations of SDHB mutation carriers.

Patients and methods

This study included all SDHB mutation carriers (18 index cases from 20 non-consanguineous families) who were prospectively followed at the department of Endocrinology and Metabolic Diseases, University Medical Center Groningen, The Netherlands.

Results

Eighty-three SDHB mutation carriers (33 men and 50 women) were included. Twenty-three mutation carriers (28%) had a manifestation, of whom 18 carriers (22%) were index patients. First manifestations included HNPG (n=15), sympathetic PGL (n=9) and phaeochromocytoma (n=1), with an overall penetrance 35% at the age of 60 years. The optimal age to start surveillance for HNPG was age 24 years, with a subsequent interval of 4 years.

Conclusion

This study emphasises a relatively low penetrance of disease in SDHB mutation carriers. By using a Poisson distribution model a more accurate estimation of the age to initiate surveillance and subsequent intervals is provided for HNPG, suggesting that guideline recommendation regarding the screening of these mutation carriers might need to be revised.

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**Endocrine tumours and neoplasia - General**

**GP.30.01**

Temozolomide treatment for pituitary aggressive tumours and pituitary carcinomas: initial results and long-term follow-up of a cohort of 32 cases

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Context

Successful use of temozolomide (TMZ) treatment has been described in 40–50% of aggressive pituitary tumour (PT) or rare pituitary carcinoma. These results are based on 50 case-reports and small series, data on long-term follow-up being rare.

Objectives

To describe initial results and long-term follow-up of a large French cohort of patients presenting PT treated with temozolomide.

Design

Members of the French Society of Endocrinology were surveyed regarding the clinical characteristics of PT treated with TMZ. Hormone and tumour responses to treatment were evaluated after three to six cycles and at the last follow-up.

Patients

32 patients (M=20) from 16 centers, 19 aggressive PT, 13 carcinomas including 16 ACTH, 12 PRL, and four GH-secreting tumours were followed 21.7±18 months after the treatment.

Results

Age at diagnosis was 42.8±19 years. All patients underwent radiotherapy, 28/32 pituitary surgeries (1–5). TMZ, 150–200 mg/m²/day, was initiated (with radiotherapy in five cases) 8.2±7.5 years after diagnosis for 8.4 cycles (3–24). Tolerance was good (thrombopenia, n=3 and pancytopenia, n=2). Overall, early response was noted in 18/32 (56.3%) with similar rate between ACTH (56%) and PRL (58%), lower for GH (50%) and higher rate in adenomas (63%) than carcinomas (46%). End of treatment response was maintained in only 13/18 patients after 10.2±5.6 cycles. No initial resistant cases responded to TMZ after 6.6±4.4 cycles. Among the 18 responders, four were in remission (three ACTH) after 30±13 months, regrowth was noted in ten patients 18–21 months after TMZ administration. Second try of TMZ failed in all cases (n=7). 8/14 resistant cases decreased compared to 2/18 initially sensitive cases. In case of TMZ failure, carboplatin-VP16, cisplatin/vedlabilutine, everolimus have been tested without significant effect.

Conclusion

Initial PT response to TMZ is frequent but long-term control or remission is rare. This study underlined lack of homogeneous therapeutic protocol and the need for guideline.

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GP 30.02
Clinicopathological significance of fractional allelic loss in prognosis of follicular cell-derived thyroid tumours
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The genetic instability, i.e. loss of heterozygosity (LOH) and microsatellite instability (MSI) are frequent molecular events in thyroid tumour aetopathogen esis. They were found in several chromosomal critical areas, including 3p12–21.2, 3p24.2–p25.3, 7q21.1–q31.2, 10q22–24, and 15q11–q13, with loci of oncogenes and tumour suppressor genes.

Aim of the study
Evaluation of usefulness of LOH/MSI as diagnostic/prognostic biomarker in follicular cell-derived thyroid tumours.

Materials
Thyroid tumour and macroscopically unchanged tissues (control) obtained from 93 patients with: follicular adenoma (F; n = 11), papillary thyroid carcinoma (PTC; n = 31), follicular thyroid carcinoma (FTC; n = 18), and nodular goitres (NG; n = 38).

Methods
Ten microsatellite markers linked with regions 1p31.2, 3p21.3, 3p24.2, 11p15.5, 11p15.5, and 16q22.1 were amplified in PCRs and then allelotyped. Fractional allelic loss (FAL) values defined as LOH/MSI coincidence in various chromosomal regions were assessed.

Results
LOH/MSI frequency was the highest in 3p21.3–3p24.2 (15%) and 11p15.5 (14.29%), followed by 1p31.2, 2p21.3 (12%), and 16q22.1 (10.25%). Statistical analysis of LOH/MSI frequency in PTC revealed significantly increased LOH/MSI in 1p31.2 (P = 0.028). Significantly increased LOH/MSI in 3p21.3 was found for pT1 tumours, AJCC stage I and tumours with diameter < 10 mm; in 1p31.2: for pT2–T4, stages II–IV, and tumours with diameter 10–30 mm; in 11p15.5: for pT2–T4, stages II–IV, and tumours with diameter > 30 mm (P < 0.05). Mean FAL values were significantly higher in men (P = 0.002), and in younger patients (< 40 years, P = 0.016). FAL was significantly higher in: FA and FTC compared with NG and FTC (P = 0.033); pT2–T4 vs pT1 (P = 0.021). Increased FAL value significantly correlated with increased tumour diameter (P = 0.044).

Conclusions
Our findings confirmed LOH/MSI occurrence in 3p21.3 at early stage of tumourigenesis while in 1p31.2 and 11p15.5, not recognised as critical areas, seems to be characteristic for advanced stage of thyroid tumours. FAL defined as LOH/MSI coincidence in various chromosomal regions may be useful biomarker in prediction of tumour progression. The increased FAL values in FA/FTC can be regarded as promising distinguishing biomarker from FTC and NG.

Disclosure
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GP 30.03
The role of androgen receptor in glucose transporters expression in prostate cancer cells
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Cancer cells show different metabolic requirements than normal cells, being the high rate of glucose uptake one of the most important aspects. An increase in glucose uptake has been associated mainly with GLUT1 overexpression but may also involve other transporters including GLUT4, whose presence in prostate cancer cells was recently discovered in our laboratory. Moreover, androgens stimulate anabolic synthesis and increase glucose uptake. Despite this, the regulation of GLUT transporters by androgens has been scarcely studied. Thus, the aim of this work was to study the relation between GLUT1/4 and the androgen receptor (AR) signalling pathway in prostate cancer cells. GLUT1/4 and AR protein levels were analysed by immunohistochemistry. Glucose uptake and glucose concentration in culture media were measured using 2-deoxyglucose and a glucometer respectively. The analysis of cell cycle was performed by flow cytometry. Finally, cell viability and proliferation were estimated by MITT reduction and Hoechst staining. Results show that GLUT1/4 expression is dependent of glucose concentration in culture media. GLUT1 was overexpressed when glucose concentration was reduced in the androgen-sensitive LnCaP and PC-3AR cells, being the number of cells in G1 phase lower. Glucose consumption was also higher in PC-3AR cells than in androgen-insensitive PC-3 cells. On the other hand, the effect of insulin (that stimulates GLUT4 transport) or indinavir (that inhibits GLUT4) were higher in androgen-insensitive cells. Moreover, AR signalling was involved in GLUT expression. Nuclear translocation of AR was increased at low glucose concentration correlating with the increment of GLUT1 levels. In addition, DHT stimulated glucose uptake and GLUT1 levels while bicalutamide (an androgen inhibitor) prevented this increment in androgen-sensitive LnCaP cells. In conclusion, AR pathway favours GLUT1 expression and functioning, while might be related to its carcinogenic properties in the prostate while GLUT4 transporter is more involved in glucose uptake in androgen-insensitive prostate cancer cells.

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GP 30.04
Re-introduction of type 1 iodothyronine deiodinase in renal cancer cells affects their migration and expression of adhesion-related genes
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Introduction
Type I iodothyronine deiodinase (DIO1) is one of the three enzymes regulating bioavailability of thyroid hormones. In contrast to DIO2 and DIO3, the specific cellular role of DIO1 remains controversial. Our previous studies showed that DIO1 expression in clear cell renal cell carcinoma (ccRCC) is decreased, followed by lower intracellular T3 concentration. In this study we explored how re-introduction of DIO1 in ccRCC cells affects their migration and proliferation.

Material
75 matched pairs of ccRCC tumours and control samples, approved by the local Bioethical Committee. Two ccRCC cell lines KIJ-265T and KIJ-308T.

Methods
ccRCC cell lines (KIJ-265T-pcDNA3-DIO1 and KIJ-308T-pcDNA3-DIO1) with stable re-expression of DIO1 and control cell lines (KIJ-265T-pcDNA3 and KIJ-308T-pcDNA3) stably transfected with empty pcDNA3 vector were generated. The expression of genes involved in adhesion and ECM were analysed with RT2 Profiler PCR Array (SA Biosciences), followed by SYBR Green/PCR validation. Scratch test and Cell Proliferation ELISA, BrdU were used for analysis of migration and proliferation respectively.

Results/conclusions
Expression of collagen COL1A1 and integrin ITGB2 was elevated in ccRCC tumours compared with control samples. Re-expression of DIO1 in KIJ-265T (grade IV) and KIJ-308T (grade II) cell lines resulted in decreased expression of COL1A1 (74 and 68% respectively) and ITGB2 (58 and 34% respectively). Scratch test revealed that migration of KIJ-265 was stimulated by DIO1 expression while in KIJ-308T DIO1 had no effect. Proliferation of both cells was reduced by DIO1 expression. We show, for the first time, that DIO1 has opposite roles in ccRCC tumourigenesis: it reduces proliferation with concomitant stimulation of migration in higher tumour grade cells. This effect is probably mediated by DIO1-induced changes in expression of genes involved in cellular adhesion. The specific mechanisms of DIO1 action in ccRCC require further investigation.

Disclosure
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**Endocrine Abstracts (2015) Vol 37**

**GP.30.05**

**Targeted destruction of FSHR-positive cells by lytic peptide Phor21 conjugated with FSH subunit in vitro**

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FSH receptor (FSHR) expression has been shown in gonadal tumours, as well as in endothelial tumour vessel cells of various cancers. FSHR, due to its transmembrane localization could be a good candidate for receptor-mediated targeted cancer therapy. In recent years, a number of membrane disrupting lytic peptides have been used for receptor-based cancer therapy. In the present study, we characterised the specificity and cytotoxicity of a lytic peptide Phor21 conjugated to three different amino-acid (AA) sequence fragments of the FSHβ chain (AA33–53, AA81–95, and AA53–81+95) with several enhancing modifications of the peptides, to ablate FSHR-positive cells in vitro. As there exists no cancer cell lines expressing functional endogenous FSHR, Phor21-FSHβ conjugates were tested in a human FSHR cDNA-stably transfected HEK293 cell line (FSHR-positive cell) and HEK293 (FSHR-negative cells). Conjugate-mediated cytotoxicity was assessed by measurement of lactate dehydrogenase (LDH), a stable cytosolic enzyme that is released upon membrane disruption by lytic peptide. Conjugate of Phor21 linked to FSHβ (AA33–53) which cysteine (Cys53) was replaced by serine (Ser) and stabilized with N-terminal amino group (Phor21-FSHβ33–53Cy5/Ser-CONH) displayed the highest specific cytotoxicity to FSHR-positive cells vs. any other tested compound. Phor21-FSHβ33–53Cy5/Ser-CONH conjugate showed in a dose dependent manner (0.5, 1.2, 2.5, and 5 μM) two- to ten fold higher ability to destroy the FSHR-positive cells than Phor21 alone. Pre-incubation or co-treatment competitive studies in FSHR-positive cells with recombinant human FSH 100 IU/L significantly decreased the cytotoxicity of Phor21-FSHβ33–53-Cys/Ser-CONH conjugate at two lowest concentrations (0.25 and 0.5 μM). Conjugating FSHβ fragment sequences to Phor21 slightly enhanced their cytotoxic effects in comparison to Phor21 backbone in FSHR-negative cells. Our results prove the principle that Phor21-FSHβ33–53-Cys/Ser-CONH may provide a novel specific therapeutic lead into targeted destruction of FSHR expressing cancer cells in vitro and as well for further in vivo studies.

Disclosure

Polish National Science Centre (2012/05/B/NZ5/01867), Academy of Finland.

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**GP.30.06**

**The Wnt/β-catenin pathway regulates the expression of early embryonic stem cell genes in human parathyroid tumours**

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Though there is no evidence of a constitutive nuclear accumulation of β-catenin, the Wnt/β-catenin pathway might be deregulated in parathyroid tumours. We investigated phosphorylated active β-catenin distribution by western blot in 16 typical parathyroid adenomas (PAds); β-catenin accumulation in the nuclear protein fractions varied from the levels detected in Caco-2 cells with constitutively active Wnt signalling (three PAds) to the levels measured in HEK293 cells with intact Wnt signalling (six PAds) and positively correlated with AXIN2 mRNA levels (r = 0.546, P = 0.03). The Wnt/β-catenin pathway is intimately connected to the embryonic pluripotent core circuitry. Therefore, we treated PAds-derived cells (n = 5) with 10–20 mM lithium chloride for 72 h: we detected nuclear accumulation of β-catenin and concurrent increases in mRNA levels of NANOG, decreases of SOX2, no changes of POU5F1/OCT4. In PAds nuclear β-catenin levels positively correlated with the NANOG mRNA levels and negatively with the SOX2 mRNA levels. Immunohistochemistry of tumour sections (11 PAds and eight carcinomas (PCas)) identified cells expressing at nuclear level the stem cell genes: NANOG-expressing cells were more abundant in parathyroid carcinomas (40.0 ± 5.8%; range 30–70%) than in PAds (11.4 ± 4.5%; range 1–40%; P = 0.01), while OCT4 was similarly detected in ~5–20% of cells in both PAds and PCas and 42% of PCas showed SOX2-expressing cells. SOX2-expressing cells were more abundant in PAds than in PCas (15.8 ± 5.9% vs 7.0 ± 3.6%; P = 0.05). Patients harbouring the PAds with detectable SOX2 transcripts (n = 22) had a more severe hyperparathyroidism at diagnosis: serum PTH and calcium levels were higher than that in patients with SOX2-undetectable PAds (n = 14): PTH: 324.2 ± 248.0 pg/ml vs 150 ± 56.0 pg/ml; P = 0.014; calcium: 11.9 ± 1.2 mg/dl vs 11.2 ± 0.7 mg/dl, P = 0.06). Immunofluorescence detected several cell coexpressing SOX2 and NANOG or OCT4, while parathyroid tumour cells expressing FTH were negative for all the stem cell genes. In conclusion, we firstly showed that i) a subset of parathyroid tumour cells express the pluripotent stem cell genes and ii) β-catenin might be involved in the regulation of the stem-like phenotype acquisition by a subset of parathyroid tumour cells.

Disclosure

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**GP.30.07**

**Steroid metabolome analysis reveals that prostate cancer has potent 5α-reductase, 3z- and 17β-hydroxysteroid dehydrogenase activities, but lacks 17-hydroxylase/17,20-lyase**

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Introduction

Prostate cancer (PC) is dependent on androgen receptor (AR) activation by its canonical ligands testosterone and 5α-dihydrotestosterone (DHT). Intratumoural androgens persisting after castration give rise to castration-resistant PC (CRPC). These intraprostatic androgen levels are hypothesized to result from either adrenal androgen conversion or intratumoral de novo DHT synthesis through the classic or alternative pathways. Quantifying the steroid fluxes responsible for CRPC development can help optimize current endocrine treatment strategies.

Methods

Five PC cell lines were incubated with 1 μM of 16 steroid intermediates of the classic and alternative androgen synthesis pathways. A PC steroid metabolome was constructed through measurement of steroid metabolite concentrations with liquid chromatography/tandem mass spectrometry (LC–MS/MS). Steroidogenic enzyme expression was estimated by quantitative PCR.

Results

Steroid metabolites could be detected for up to three enzymatic steps downstream of the employed steroid substrate, 17-hydroxylase/17,20-lyase activity was undetectable in all PC cell lines with eight different substrates tested, thereby excluding conversion above 0.03% of the substrate. In contrast, 3z-, 17β-hydroxysteroid dehydrogenase and 5z-reductase activities were present in all cell lines to varying degrees. Steroid flux analysis confirmed conversion of adrenal androgen precursors and androgen metabolites into DHT. Furthermore, C21 steroids progestereone and 17hydrox-progestereone were metabolised into intermediates of the alternative pathway without reaching androsterone. The highest steroidogenic activity was observed in C4-2B cells, a castration-resistant, bone-metastasizing clone of LNCaP. Expression profiles of steroidogenic enzymes matched the observed enzymatic activities.

Conclusion

For the first time, a quantitative steroid metabolome of PC cells has been generated through LC–MS/MS, providing strong evidence against intratumoral de novo steroid synthesis. Adrenal androgens can effectively be converted into DHT, whereas precursor C21 steroids divert towards the alternative pathway. The presence of these hormones in PC might suggest a role for activity or further metabolism of alternative pathway steroids in PC evolution.

Disclosure

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E-Posters
Adrenal cortex

**EP1**

**Evaluation of cases by short synacthen test (dose: 250 µg i.v.) suspected as secondary adrenal insufficiency of prolonged steroid abuse**

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**Introduction**

Adrenal insufficiency is a common problem in our country due to steroid abuse in various forms. In many occasions the patients even do not know about its side effects and consequences of non-prescribed usage. Many of them presents with sudden withdrawal and adrenal crisis. Many of them admits in Gastroenterology unit due to vomiting, some of them in Medical unit with unexplained fever, weakness, anaemia, etc. Many of them having subtle features of Iatrogenic Cushing’s. In this case series, patients of history of chronic steroid use but, are not taking steroid at least since last 4 weeks are evaluated due to their minimal symptoms.

**Methods**

All patients having history of supraphysiological dose of steroid use more than 3 months in any form but not taking for at least 1 month. Clinically stable, not at crisis. All 34 subjects were evaluated by short synacthen test 250 µg i.v. Three samples S.cortisol were test 0 h, and after Inj. synacthen 250 µg i.v. 30 and 60 min. S.ACTH was tested with 0 min cortisol.

**Result**

At 0 h S.cortisol value ranges from 53 to 313 nmol/l. At 30 min after Inj. synacthen 250 µg i.v. S.cortisol ranges from 76 to 622 nmol/l and at 60 min 87–587 nmol/l. In the group who has 0900 h S.cortisol <140 nmol/l (n=15) they have at 0 h S.cortisol 53–411 nmol/l and at 60 min 76–527 nmol/l. S.ACTH at 0900 h was within normal limit.

**Conclusion**

In cases of suspected secondary adrenal insufficiency due to steroid use (basal S.cortisol <240 nmol/l) synacthen test with 250 µg Tetracosactren (Synacthen) i.v. mostly shows partial adrenal insufficiency. In most cases immediate replacement were depended on clinical presentation not on lab values. So for representative lab values (whom to treat or not to treat with steroid) dose of synacthen for the ‘TEST’ can be reconsidered at lower dose between 1 and 250 µg. As 1 µg is not available, preparation by self-dilution method, is got standardised in lab always. Pharmaceutical companies should be requested for standard strength of ACTH may be 10–100 µg/ml for dispensing. Further RCT with 1 µg to 10 µg can be considered to find the standard dose of the ‘Low Dose Test’.

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**EP2**

**Management of urgent surgical intervention due to coexistence of pheochromocytoma and hydrocephalus in a patient presenting with Von Hippel Lindau syndrome**

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A 41-year-old woman was admitted with headache and hypertension. She described worsening of headaches in the last 2 months. On physical examination blood pressure was 150/90 mmHg, and grade 1 hypertensive retinopathy was present. Her sister died at the age of 24 due to pancreas neuroendocrine tumour and her mother was followed up with multiple pancreatic cysts. Abdomen MRI revealed a 6 cm pheochromocytoma lesion on the right suprarenal and multiple cysts in the pancreas, kidneys and ovaries. Urinary catecholamin levels were elevated by sixfold. Other laboratory results were normal. Doxazosin 4 mg (b.i.d.) and amlopidin 5 mg were initiated. Patient’s family history, presence of multiple vesical cysts and pheochromocytoma led us to consider Von Hippel Lindau syndrome. Cranium MRI which was performed due to severe headaches revealed a 5 cm spherellar hemangioblastoma and hydrocephalus of the third ventricle. Urgent surgical intervention was indicated due to presence of hydrocephalus and risk of herniation. Coexistence of pheochromocytoma, risk of hypertensive crisis and deterioration of herniation with anaesthesia induction made it mandatory to perform the two surgeries sequentially in the same surgical session. As the patient had been receiving β blockers for a sufficient time of preoperative period, laparoscopic right suprarenalectomy was performed, followed by hemangioblastoma excision in the same session. Pathological evaluation revealed, right suprarenal pheochromocytoma with a Ki score of 3% and grade 1 spherellar hemangioblastoma. Two months after the surgery patient was normotensive without any antihypertensive treatment and symptoms of headache were omitted. Screening of the family members revealed multiple pancreas, renal and epididymal cysts, spherellar hemangioblastoma and pheochromocytoma in her brother compatible with Von Hippel Lindau syndrome and treatment was initiated. Evaluation of the other family members were normal and a surveillance programme was scheduled.

**Conclusion**

Hemangioblastoma of central nervous system which may complicate the surgery of pheochromocytoma must be considered in patients who present with pheochromocytoma and multisystemic manifestations implicating presence of a genetic syndrome.

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**EP3**

**A case of polyglandular autoimmune syndrome type 1 with hypercalcaemia and hypertension**

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Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is also known as autoimmune polyendocrine syndrome type 1 (APS-1). We present a case of autoimmune polyendocrine syndrome type 1 with hypercalcaemia of adrenal insufficiency during the calcium treatment because of hypoparathyroaidism. Case

A 20-year-old female patient was diagnosed with APS-1 in 2004. She applied to ER with the complaints of nausea and vomiting. Her laboratory findings proved hypercalcaemia, hyponatremia and hypotension. She’d had an upper respiratory infection a week prior to her application to our hospital. In her ECG, t-waves were found to be commonly inverted. Her echocardiography revealed increased pericardial brightness. Thus, indomethacin 2×1 l was started as pericardite was suspected. BP of 90/40 mmHg and dry skin were found in the physical examination. Horizontal ridges and trophic deformities on both finger nails and toes were observed (Picture 1). The laboratory findings were as follows: BUN: 58 mg/dl, creatinine: 0.82 mg/dl, Na: 127 mEq/l, K: 4.6 mEq/l, Ca: 12.6 mg/dl, FSH: 4.42 mIU/ml, LH: 5.63 mIU/ml, ACTH: 124 pg/ml, cortisol: 0.40 µg/dl, DHEAS: 4.6 µg/dl, free T3: 1.94 µg/ml, free T4: 1.07 mg/dl, TSH: 3.26 µIU/ml, anti TPO: 14.7, PTH: 0.01 pg/ml. Hypercalcaemia was associated to adrenal insufficiency. I.v. hydration and steroid of stress dose was started because of hypercalcaemia and hypotension. We applied maintenance doses of hydrocortisone (30 mg/day) and Fludrocortisone (0.1 mg×12 a day) to the improved patient. Calcitriol and calcium were restarted to the patient as her Ca level was 6.5 mg/dl in the follow-up period. The patient had a leukoplakic lesion characterized with candida plaque on the right buccal mucosa. Thus, sodium bicarbonate and mocyostain suspensions were added to the treatment.

**Discussion**

The most important components of OPS type 1 are hypoparathyroidism, Addison’s disease and candidiasis with other disease associations of hypo- thyroidism, hypogonadism and infertility, alopecia (baldness), malabsorption, chronic active (autoimmune) hepatitis. It is a genetic disorder inherited in autosomal recessive tendency due to a defect in the auto immune regulator (AIRED) gene located on chromosome 21.q22.3. In our case, hypercalcaemia was thought to develop as a result of calcitriol and calcium treatment and addition of adrenal insufficiency. One should always remember that calcitriol and calcium treatment simultaneously with adrenal crisis triggered by stress assist the development of hypercalcaemia in the cases with APECED.

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**EP4**

**The value of high effective liquid chromatography in the diagnosis of primary aldosteronism**

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EP5

Influence of glucocorticoids on markers of inflammation in community-acquired pneumonia
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Background
Glucocorticoids are frequently prescribed in inflammatory diseases. We investigated the influence of prednisone on classical and novel inflammatory markers in community-acquired pneumonia (CAP).

Methods
We evaluated levels of pro-inflammatory protein (CRP), procalcitonin, leukocyte and neutrophil count in a prospective randomized, double-blind, placebo-controlled multicenter trial which compared prednisone 50 mg for 7 days to placebo in patients hospitalized with CAP. We performed Mann-Whitney U tests to compare biomarker levels between groups on day 1 before the first administration of prednisone and thereafter on days 3, 5, 7 and discharge.

Results
335 patients in the prednisone group and 350 patients in the placebo group were evaluated. At baseline, all investigated markers levels did not differ between prednisone and placebo group. At days 3, 5, 7, and 7, CRP levels were significantly lower in the prednisone group than in the placebo group (P<0.0001 for each time point). At hospital discharge, CRP levels were similar (P=0.53). For procalcitonin, this attenuating effect of steroids on circulating levels was not visible (P>0.05 for all points). Leukocyte and neutrophil count were higher in the prednisone group during administration of glucocorticoids (P<0.0001 for all time points including discharge).

Discussion
Administration of glucocorticoids in patients with CAP lowers CRP levels and increases leukocyte and neutrophil count, but has no influence on procalcitonin levels. Therefore, procalcitonin may be a more adequate inflammatory marker to measure treatment response in patients with an infectious disease receiving glucocorticoids.

Disclosure
This work was supported by the Swiss National Science Foundation (grant numbers P50P3_123546, P2BSP3_155212, PP00P3_150531/L, 320030-138267, and 320030-150025), the Nora von Mueven Höffiger Stiftung, the Gottfried Bangerter-Rhyner Stift.

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EP6

Clinical and pathological characteristics of hypertensive and normotensive adrenal phaeochromocytomas
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Context
Distinct differences of clinical manifestations exist in hypertensive phaeochromocytomas (HPs) and normotensive phaeochromocytomas (NPs), however the comparative analysis is lacking.

Objective
The objective of the study was to assess the clinical symptoms, haemodynamics, metabolism, radiological and histological features of patients with HPs and NPs.

Research design and methods
This retrospective study included 104 patients who underwent a unilateral adrenalectomy with a diagnosis of phaeochromocytoma at the Drum Tower Hospital Affiliated to Nanjing University Medical School from January 2004 to December 2014. All available clinical, biochemical, and radiological records were reviewed in phaeochromocytoma patients who were then categorized into HPs (n=69) and NPs (n=35) groups. Tumour samples were examined to determine the adrenal gland scale score and were available for measurement of gene transcriptions. Clinical and biochemical examinations of consecutive 95 subjects with primary hypertension (PH) were recorded for comparative study.

Results
Patients with NPs showed lower proportion of clinical triad, inapparent metabolic disorders and lower urinary catecholamine levels than HPs, but higher than PH. Tumour weight positively correlated with 24 h urinary norepinephrine level in patients with HPs (P=0.028) and tumour diameter negatively correlated with phenylethanolamine-N-methyltransferase (PNMT) immunohistochemistry (P<0.01) in NPs but not in HPs. The adrenal gland scale score of NPs group was similar to that of HPs group. The positive percentage of E-type of catecholamine in HPs group was higher than that in the NPs, while the positive percentage of NE-type or no function of catecholamine in HPs group was lower than that of the NPs. The transcript levels of PNMT, secretogranin II (SGII) and neuromedin Y (NPy) from tissue samples were significantly lower in NPs than in HPs, while vesicular monoamine transporter 1 (VMAT1) had no difference between HPs and NPs.

Conclusions
HPs and NPs have distinct differences in clinical, biochemical and pathological phenotypes, which are closely related with the catecholamine pathway productions involved in tumour occurrence and development.

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EP7

New onset sarcoidosis after remission of Cushing’s syndrome
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Introduction
Glucocorticoids, even endogenous or exogenous, suppress the inflammatory response therefore they are the most preferred treatment options in inflammatory diseases. Persistent hypercortisolism induces lymphopenia and lymphoid tissue atrophy. Excessive endogenous hypercortisolism might mask the active inflammatory disease. Rebound immune modulation may occur after Cushing’s syndrome (CS) remission, leading to the new onset of autoimmune diseases.

Case
Here, we report a 27-year-old female patient newly diagnosed as sarcoidosis after remission of CS. Adrenal CS was treated successfully with right adrenalectomy. The patient was free of sarcoidosis during the course of CS with normal thorax imaging and without any symptoms of sarcoidosis. After complete remission of
CS she started to complain of cough and was diagnosed sarcoidosis with clinical, radiological and bronchoscopic evidence.

Conclusion
Endogenous Cushing’s syndrome is caused either by excess ACTH secretion or by autonomous cortisol release from the adrenal cortex. Glucocorticoids are the main endogenous mechanism to suppress the inflammatory response genes. Exposure to persistent hypercortisolism induces lymphopenia and lymphoid tissue atrophy resulting in immunosuppression. After treatment of CS rebound immunity occurs especially in patients with overt disease. In rare cases, the treatment of CS may result in unmasking or aggravation of diseases responsive to glucocorticoid medication such as thyroid, rheumatologic and allergic diseases. Excessive hypercortisolism might suppress the active inflammatory stage of sarcoidosis. However, the disease became apparent after the reduction of cortisol levels following the treatment of CS.

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EP8

Extra-adrenal myelolipomas in association with cortisol hypersecretion

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Extra-adrenal perirenal myelolipoma has been reported since 1980. In recent years, it has been reported at an increasing rate in different sites of the body ranging from the nasal cavity, mediastinum to preaerial, paraaerial region. However, it was the first reported case that perirenal multiple myelolipomas, each myelolipoma was about 5 cm in diameter, in association with cortisol hypersecretion. A patient was an emigrant. She was followed in her country and was prescribed ketokonazol. She did not take her medicine and she was brought to emergency service when her situation deteriorated. She was exposed to hypercortisolism for a long time and had severe muscle weakness, fatigue, amenorrhea and weight loss at admitted-time. Physical examination revealed cushingoid appearance with trunk obesity, sebaceous moon face, hirsutism, muscle wasting, high blood pressure, acanthosis nigricans and abdominal striae. Laboratory tests were as following: glucose: 170 mg/dl (70–100), urea:42.3 mg/dl (17–43), creatinin: 0.82 mg/dl (0.5–0.95), sedimentation: 35 mm/h (0–30), HbA1c: 8.8%, FSH: 1.59 mIU/ml (4.54–22.51), LH: 0.31 mIU/ml (12–12.86 mIU/ml), estradiol: 16 pg/ml (49–291), progesterone: 1.75 ng/ml (5.16–18.56), total testosterone: 0.48 pg/ml (0.1–0.75), cortisol: 30.40 pg/dl (6.7–22.6), ACTH: <1 pg/ml (7.2–63.5). Eosinopenia, lymphocytopenia and neutrophiilia was obtained in whole blood cell evaluation. Cortisol level was 27.60 µg/dl after 1 mg dexamethasone suppression test, result revealed failure of suppression. Pituitary MR was normal. A contrast enhanced abdominal MR showed multiple lobulated bilateral perirenal masses and a cystic mass at the caput of the pancreas without solid component. A contrast enhanced abdominal MR showed multipl lobulated bilateral perirenal masses for phaeochromocytoma.

Extra-adrenal perirenal myelolipoma has been reported since 1980. In recent years, it has been reported at an increasing rate in different sites of the body ranging from the nasal cavity, mediastinum to preaerial, paraaerial region. However, it was the first reported case that perirenal multiple myelolipomas, each myelolipoma was about 5 cm in diameter, in association with cortisol hypersecretion. A patient was an emigrant. She was followed in her country and was prescribed ketokonazol. She did not take her medicine and she was brought to emergency service when her situation deteriorated. She was exposed to hypercortisolism for a long time and had severe muscle weakness, fatigue, amenorrhea and weight loss at admitted-time. Physical examination revealed cushingoid appearance with trunk obesity, sebaceous moon face, hirsutism, muscle wasting, high blood pressure, acanthosis nigricans and abdominal striae. Laboratory tests were as following: glucose: 170 mg/dl (70–100), urea:42.3 mg/dl (17–43), creatinin: 0.82 mg/dl (0.5–0.95), sedimentation: 35 mm/h (0–30), HbA1c: 8.8%, FSH: 1.59 mIU/ml (4.54–22.51), LH: 0.31 mIU/ml (12–12.86 mIU/ml), estradiol: 16 pg/ml (49–291), progesterone: 1.75 ng/ml (5.16–18.56), total testosterone: 0.48 pg/ml (0.1–0.75), cortisol: 30.40 pg/dl (6.7–22.6), ACTH: <1 pg/ml (7.2–63.5). Eosinopenia, lymphocytopenia and neutrophiilia was obtained in whole blood cell evaluation. Cortisol level was 27.60 µg/dl after 1 mg dexamethasone suppression test, result revealed failure of suppression. Pituitary MR was normal. A contrast enhanced abdominal MR showed multiple lobulated bilateral perirenal masses and a cystic mass at the caput of the pancreas without solid component. A contrast enhanced abdominal MR showed multipl lobulated bilateral perirenal masses and a cystic mass at the caput of the pancreas without solid component. A contrast enhanced abdominal MR showed multipl lobulated bilateral perirenal masses and a cystic mass at the caput of the pancreas without solid component. A contrast enhanced abdominal MR showed multipl lobulated bilateral perirenal masses and a cystic mass at the caput of the pancreas without solid component. A contrast enhanced abdominal MR showed multipl lobulated bilateral perirenal masses and a cystic mass at the caput of the pancreas without solid component. A contrast enhanced abdominal MR showed multipl lobulated bilateral perirenal masses and a cystic mass at the caput of the pancreas without solid component. A contrast enhanced abdominal MR showed multipl lobulated bilateral perirenal masses and a cystic mass at the caput of the pancreas without solid component. A contrast enhanced abdominal MR showed multipl lobulated bilateral perirenal masses and a cystic mass at the caput of the pancreas without solid component. A contrast enhanced abdominal MR showed multipl lobulated bilateral perirenal masses and a cystic mass at the caput of the pancreas without solid component.

The patient groups of the study consisted of 18 Cushing’s syndrome patients, 12 patients with non-functional adrenal incidentaloma, 37 patients with obesity, 16 patients with hirsutism and 26 healthy control patients. Salivary cortisol (SC) and plasma cortisol after 1 mg-overnight DST were measured. SC was measured with lucidense immunoassay kit.

Results
Salivary cortisol levels after overnight DST was found significantly different between all groups (P<0.05) except between patients with hirsutism and obesity and between patients with adrenal incidentaloma and healthy control group (P=0.357). In this context, plasma cortisol levels after overnight DST were not significantly different between patients with hirsutism and control group and between patients with obesity and control patients both, while it was significantly different between all the other groups.

When all the patient groups are evaluated in a whole group there was a significant positive correlation between plasma and salivary cortisol (r=0.542, P=0.0001). In the subgroup analyses, there was no correlation between salivary and plasma cortisol in patients with hirsutism and Cushing’s syndrome. In the groups with adrenal incidentaloma and healthy control, highly significant correlation between salivary and plasma cortisol was found (r=0.750 – P=0.02, r=0.679 – P=0.008 respectively).

Conclusion
Salivary cortisol after overnight DST may be one of the new non-invasive diagnostic tools for the differential diagnosis of Cushing’s syndrome and pseudo-Cushing syndrome. However, laboratory test results and clinical findings should be evaluated together in clinical practice.

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EP10

Overview of phaeochromocytomas at Vilnius University Hospital Santariskiu clinics (VUHSC): 5 year results

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The aim of our study was to estimate the prevalence and describe diagnosis, treatment and follow up strategy of phaeochromocytomas at VUHSC.

Results
There were 702 patients diagnosed with adrenal masses from 2010 to 2014. Only half of patients were screened for phaeochromocytoma which included 24 (the incidence is 3.4%). Phaeochromocytoma was diagnosed in 5 (20.8%) males and 19 (79.2%) females, average age 55±11.5 years. After surgery 2 (8.3%) were confirmed as paragangliomas. Although there were 21 (87.5%) symptomatic patient – most commonly with hypertension – 16 (66.7%), episodic tachycardia – 13 (54.2%), episodic elevations of blood pressure – 12 (50.0%) and sweating – 4 (16.7%), phaeochromocytoma was found incidentally in 15 (62.5%) cases. The average tumour size of 48.0±23.4 mm and density of 33.7±11.6 HV was estimated by computed tomography performed for all patients. Most tumours were found in the left adrenal – 15 (62.5%), bilaterally – in 1 (4.2%) patient. In 45.8% of cases scintigraphy with iodine-123-metaiodobenzylguanidine was performed and uptake confirmed in all suspected tumours. Hormonal activity was confirmed in 20 (83.3%) cases by elevation of plasma metanephrine and/or normetanephrine or urine/plasma adrenaline and/or noradrenaline. Isolated elevations of either adrenaline or metanephrine was detected in 4 (16.7%), noradrenaline or normetanephrine – in 3 (12.5%) cases. Adrenalectomy was performed in 21 (87.5%) patient with suspicion of malignant tumour in 9 (42.9%) cases of after histological examination. Two of them received chemotherapy, but were diagnosed with the recurrence of disease, others are under follow up with no disease relapse. Genetic syndromes were diagnosed in 2 (8.3%) subjects: Von Hippel Lindau syndrome and type 1 neurofibromatosis.

Conclusions
The incidence of phaeochromocytoma in our hospital is 3.4% and meets the rates estimated by others. High prevalence of asymptomatic patients and suspicion of malignant tumours after histology urge for careful assessment of all adrenal masses for phaeochromocytoma.

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EP11
Aldosterone- and cortisol co-secretion in adrenal adenoma in an adolescent girl: a case report
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Introduction
Primary aldosteronism (PA) is the most common reason for secondary hypertension. Among adrenal disorders, rarely aldosterone- and cortisol-co-secretion adenomas (ACPA) can lead to PA. 35 patients with ACPA were reported to date and their mean age was 52 (range 34–80) years. We report an ACPA in an adolescent girl presenting with hypertension combined with hypokalemia and signs of hypercortisolism.

Case report
A 18-year-old girl admitted to endocrinology outpatient clinic with the complaint of hypertension. Physical examination revealed central obesity (BMI:31 kg/m²), moon face, hirsutism, buffalo hump and abdominal striae. Her blood pressure was 170/110 mmHg. Laboratory examination revealed serum potassium level of 2.4 mEq/l. The mean aldosterone to renin ratio was 308 (aldosterone: 98.77 ng/dl, plasma renin activity (PRA): 0.32 ng/ml per h). Intravenous saline infusion test was performed as the confirmatory test. Her post-infusion aldosterone level was 80.69 ng/dl. While the midnight serum cortisol level was 7.6 μg/dl, her serum cortisol levels failed to suppress during a 1 mg dexamethasone suppression test (DST) (5 μg/dl) and 2 mg DST (9.8 μg/dl). Serum ACTH and DHEA-S levels were 13.1 pg/ml and 11.12 μg/dl (nr: 65–368) respectively. Computed tomography of adrenal glands revealed a 24×14 mm hypodense solid lesion in the right adrenal gland. She underwent laparoscopic right adrenalectomy with perioperative steroid replacement. At the postoperative day 4 at 0800 h, serum cortisol level was 0.6 μg/dl and she was put on substitution therapy with oral glucocorticoids. The aldosterone level and PRA were 2.12 ng/dl and 5.59 ng/ml per h 2 days after the operation, respectively. At the follow-up, her blood pressure and serum potassium level returned to normal.

Conclusion
Patients with ACPA may present with overt or subclinical hypercortisolism. Therefore, pre-operative screening of cortisol co-secretion in patients with aldosterone-producing adenomas is important to prevent adrenal crises at the perioperative period.

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EP13
Does IGF-1 have a role in etiopathogenesis of adrenal incidentaloma?
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Objective
Due to increased usage of imaging modalities today, incidence of adrenal incidentaloma (AI) has increased. Insulin resistance is considered as the etiopathogenic mechanism. Since both insulin and IGF-1 are capable of interacting with same receptors, we aimed to investigate whether IGF-1 has a role in development of adrenal incidentaloma.

Materials and method
50 female patients with nonfunctional adrenal incidentaloma and 55 acromegaly patients (20 male, 35 female) that admitted to endocrinology outpatient ward between 01/08/2012 and 01/01/2014 and have had undergone abdominal CT or MRI scan were included in this study in addition to a control group of 38 female patients who had performed abdominal CT scan due to urolithiasis. Those patients in adrenal, acromegaly and control groups were assessed regarding age, BMI, waist circumference and serum IGF-1 levels.

Results
Regarding age, no significant difference was present between three groups. BMI and waist circumference (WC) in the control group was lower than those in the acromegaly and adrenal groups (P<0.001). Although BMI and WC values were higher in adrenal group, IGF-1 values were significantly higher when compared to the control group (P<0.001). Prevalence of adrenal incidentaloma was found to be significantly higher in the acromegaly patients than the control group (25% vs 3%). The results were similar when male patients in acromegaly group were excluded and analysis was conducted only among female subjects. Adrenal incidentaloma prevalence in female acromegaly patients was 34% whereas in the control group it was 3%.

Discussion
In this study, our findings of elevated serum IGF-1 levels in nonfunctional AI patients and higher prevalence of adrenal incidentaloma in acromegaly patients when compared to control group let us think that IGF-1 has a role in the etiopathogenesis of adrenal incidentaloma.

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EP14
Effects of megestrol acetate on adrenal function and survival in cancer patients
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Introduction
Megestrol acetate (MA) has been used in various cancers as a palliative agent to treat cancer cachexia. It has glucocorticoid activity and can induce significant secondary adrenal suppression. We designed this study to determine the extent of adrenal insufficiency in cancer patients receiving MA and find out whether there was any predictive factor for this.

Methods
Thirty-one patients (11 females and 20 males, aged 48–83 years) who were receiving MA took part in this study. They were evaluated for HPA axis; before the initiation and 1 month later. Serum concentrations of TSH, ACTH, free T4, cortisol were measured in samples obtained at 0700 h, at baseline and 1 month. Standard ACTH (250 mg) stimulation test was performed if cortisol levels were below 18 μg/dl at any time.

Results
1 month after drug initiation, 32% of patients were accepted as adrenal insufficient. There wasn’t any correlation between the basal cortisol, ACTH levels, any biochemical parameter and overall survival. There was negative correlation between 1 month cortisol levels and survival time (P=0.04). If cortisol levels were lower at month of therapy survival time was longer. Cox regression analysis showed that patients having lower cortisol levels at first month had 98% lower risk of death compared to patients having higher cortisol levels (P=0.02; OR 0.12 (0.02–0.75)).
Case report
A 61-year-old male farmer was referred for evaluation of a mass in the right supraclavicular region and a left adrenal lesion. The patient had a history of a multifocal papillary and medullary thyroid carcinoma 3 years before presentation. Genetic analysis for RET mutations was negative. Laboratory tests revealed increased 24-h urinary dopamine and also increased serum calcitonin and neuron specific enolase. The adrenal lesion measured 88.5 mm on MRI, displayed inhomogeneous enhancement of the contrast agent and low diffusion rate. Both lesions appeared positive in 111-Pentetetide scintigraphy, while metaiodobenzylguanidine (MIBG) scintigraphy was negative. Pathologic examination of the resected right supraclavicular mass and left adrenal was consistent with malignant melanoma. Rough evaluation for a primary melanoma site was negative.

Conclusion
This is the case of a possibly primary adrenal malignant melanoma with imaging and biochemical features of a phaeochromocytoma. Melanocytes and chromaffin cells share a common embryological origin and in melanoma tissue there is expression of tyrosine hydroxylase leading to production of DOPA and melamins. Although this case is very rare, and there are rigid diagnostic criteria for the diagnosis of primary adrenal melanoma, the differential diagnosis of a dopamine secreting adrenal mass should include primary or metastatic malignant melanoma in order to determine the best diagnostic approach to the patient and select the most appropriate surgical management.

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EP15

The effect of retinoic acid on human adrenal corticosteroid secretion in vitro
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Retinoic acid, a derivative of vitamin A, has recently yielded promising results in the treatment of Cushing’s disease (Pecori Giraldi et al. JCEM 2012). Its main site of action appears to be the tumoral corticosterone as retinoic acid inhibits POMC transcription and corticosterone proliferation (Paez-Pe reda et al. JCI 2001). Studies on tumoural adrenal cell lines have revealed an additional inhibitory effect on cell proliferation and stimulated corticosteroid secretion (Paez-Pe reda et al. JCI 2001).

Aim
The aim of the current study was to evaluate whether retinoic acid modulates corticosteroid secretion by normal human adrenals in vitro.

Methods
Primary cultures from nine normal human adrenals were incubated with 10 nM, 100 nM and 1 µM retinoic acid with and without 10 nM ACTH for 24 h. Cortisol levels in medium were measured by Coat-A-Count RIA (Siemens Healthcare Diagnostics, Erlangen, Germany); CYP11A, STAR and MC2R gene expression were analyzed by real-time PCR (7900 HT Sequence Detection System, Applied Biosystems, Foster City, USA) normalized to RPLP0.

Results
A clear-cut increase in cortisol secretion during retinoic acid incubation was observed in five adrenal specimens (10 nM: 183.9 ± 55.9%, 100 nM: 210.1 ± 82.6% and 1 µM: 141.3 ± 11.7% baseline). Gene expression analysis revealed a marked decrease in MC2R expression (10 nM: 0.65 ± 0.13, 100 nM: 0.63 ± 0.09 and 1 µM: 0.55 ± 0.08 over baseline) and an increase in STAR in cells treated with retinoic acid (10 nM: 1.53 ± 0.26, 100 nM: 1.62 ± 0.17 and 1 µM: 1.63 ± 0.16 over baseline). CYP11A was on average unchanged by retinoic acid. Incubation with ACTH led to a marked increase in cortisol secretion and in CYP11A, STAR and MC2R expression. Retinoic acid and ACTH co-incubation resulted in a slightly greater cortisol release (10 nM: 125.4 ± 16.6%, 100 nM: 141.1 ± 29.5% and 1 µM: 139.6 ± 31.3% ACTH) and MC2R inhibition (10 nM: 0.76 ± 0.13, 100 nM: 0.56 ± 0.07 and 1 µM: 0.64 ± 0.09 over ACTH) than ACTH alone.

Conclusions
Retinoic acid exerts a stimulatory effect on adrenal corticosteroid secretion in vitro, activates STAR expression and blunts MC2R transcription. This paves the way for novel avenues of research in patients with Cushing’s syndrome.

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EP16

Adrenal malignant melanoma masquerading as a phaeochromocytoma
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Introduction
Adrenal masses usually represent benign and nonfunctional adrenal adenomas however, primary or metastatic malignancy should also be considered. Discovery of an adrenal mass needs further evaluation in order to exclude malignancy and hormonal secretion. Primary adrenal melanoma is an extremely rare entity, while metastases of cutaneous melanoma to the adrenals occur much more often. We present a rare case of a possibly primary adrenal malignant melanoma with imaging and biochemical features of a phaeochromocytoma.

Conclusions
Our patients reproduce well referenced data from other series. Hiperandrogenism was the main cause of consultation.

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**EP18**

**Subclinical Cushing’s syndrome and clinical implications in bilateral compared to unilateral adrenal incidentalomas: a meta-analysis**

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**Introduction**

The aim of this study was to systematically review the literature for studies that have investigated possible differences in prevalence of subclinical Cushing’s syndrome (SCS) and related clinical implications between patients with unilateral (UAI) and bilateral adrenal incidentalomas (BAI) and to meta-analyze the best evidence available.

**Methods**

Electronic databases PubMed, MEDLINE and EMBASE were systematically searched. Main study outcome was the prevalence of SCS in patients with UAI and BAI. Secondary outcomes were the prevalence of obesity, diabetes, glucose intolerance, hypertension, dyslipidaemia and osteoporosis in patients with UAI and BAI. Random effects odds ratios (OR) or standardized mean differences (SMD) and 95% CI were calculated. Meta-analysis was conducted using Review Manager (RevMan 5.3).

**Results**

Six studies were included in the meta-analysis involving in total 1239 patients, 968 with UAI and 271 with BAI. Patients with UAI had lower prevalence of SCS compared with those with BAI (OR (95% CI) 0.51 (0.32; 0.81), $I^2 = 55\%$). The mass diameter of UAI did not differ from BAI (the size of the largest lesion) (SMD (95% CI) $-0.40 (-0.97; 0.17)$, $I^2 = 91\%$). The prevalence of obesity (SMD (95% CI) 0.06 ($-0.10; 0.22)$, $I^2 = 0\%$), diabetes (OR (95% CI) 0.78 (0.51; 1.12), $I^2 = 0\%$), hypertension (OR (95% CI) 1 (0.47; 2.12), $I^2 = 74\%$) and dyslipidaemia (OR (95% CI) 0.93 (0.49; 1.78), $I^2 = 49\%$) did not differ between UAI and BAI.

**Conclusions**

Patients with BAI present a higher prevalence of SCS compared to patients with UAI, without any differences in related clinical implications.

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**EP19**

**Association of psoriasis with Cushing’s syndrome**

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**Introduction**

Psoriasis is a chronic, inflammatory and T-cell mediated autoimmune disease of skin. Its prevalence is 2–3%. It may improve due to immunosuppressive effects of hypercortisolism during the active phase of Cushing’s syndrome (CS) and may exacerbate after treatment. The aim of this study was to investigate association of psoriasis with CS.

**Methods**

We prospectively followed 62 patients who had been diagnosed with CS between 2010 and 2014 in our clinic. Of the patients, 60% was Cushing disease (CD) (29 female, eight male) and 40% was ACTH-independent CS (20 female, five male). The patients were evaluated for psoriasis.

**Results**

The prevalence of psoriasis was 5% among our patients with CS. Psoriasis was diagnosed in three patients; two had pituitary adenoma and one had adrenal adenoma. Two were diagnosed before treatment of CD, and the other was diagnosed after 2 years following remission of ACTH-independent CS. The pathological evaluation of two patients with CD was reported as densely granulated corticotroph adenoma and the pathological evaluation of the patient with ACTH-independent CS was reported as adrenocortical adenoma with nuclear pleomorphism and possible malignant behaviour. In the light of these findings, potential hypersecretory tumours should be considered.

**Discussion**

Endogenous hypercortisolism suppresses inflammatory response and induces a state of immunosuppression. Once cortisol levels come back to normal following remission of CS, rebound response of immunity may result in exacerbation of autoimmune diseases like psoriasis. Prevalence of psoriasis is elevated in CS. If the patient is known to have a history of stress-responders psoriasis prior to surgery, we should evaluate the patient more carefully and frequently for exacerbation of psoriasis after remission of CS. Autoimmune diseases may exacerbate or may be newly diagnosed because of rebound immunity in remission of CS.

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**EP20**

**Should Cushing syndrome be only evaluated by endocrinologists and neurosurgeons?**

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**Objective**

Physical features such as central obesity, purple stria, thin skin, moon face and buffalo hump may be observed in Cushing’s syndrome (CS). Psychiatric and psychological disturbances may also be present in addition to the physical problems. The most common mental disturbance is major depression. Mania and anxiety disorders may also be seen. It may be detected both in active period or in remission of CS on account of persistent effect of previous period of hypercortisolism, hypopituitarism and glucocorticoid deficiency. In this study, we aimed to analyse the frequency of psychopathologic disorders in CS.

**Methods**

We prospectively followed 62 patients that had been diagnosed with CS between 2010 and 2014 in our clinic. Of the patients, 60% were Cushing’s disease (CD) (29 female, eight male) and 40% were ACTH-independent CS (20 female, five male). The patients who had been under medication for psychopathology were included in the study.

**Results**

The prevalence of psychopathology was 19% in CS (12 patients). In ACTH-independent CS and CD it was 12 and 24%, respectively. Eleven (92%) patients were female. Nine (75%) patients had active diseases. Two patients, one with CD and one with ACTH-independent CS, had history of suicide attempts 1.5 and 2 years after surgery, respectively. Both suicide attempts happened after surgery. The patients who attempted suicide had glucocorticoid deficiency and hypopituitarism, respectively.

**Discussion**

In CS patients, psychiatric and psychological disorders may be seen before or after treatment. Despite treatment for CS, they still may have severe psychopathologic disorders to the degree of suicide attempts due to hormonal insufficiencies in the postoperative period that may result from medication or surgical complications. For this reason, patients should be evaluated not only by endocrinology and neurosurgery clinics, but also psychiatry clinics both before and after the surgery.

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**EP21**

Necessity of thrombophylaxis in Cushing’s syndrome

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**Introduction**

Cushing’s syndrome (CS) is accompanied by a ten times increased risk of venous thromboembolism and arterial thrombosis. In this study we aimed to analyze frequency of thromboembolism in CS.

**Methods**

We prospectively followed 62 patients who had been diagnosed with CS between 2010 and 2014 in our clinic. Of the patients, 60% had Cushing’s disease (CD) (29 females and eight males) and 40% had ACTH-independent CS (20 females and five males). Frequencies of arterial and venous thromboembolic events were recorded.

**Results**

The prevalence of thromboembolic events was 5% in our patient population. Thromboembolism was diagnosed in three patients (two CD and one ectopic CS), one with venous thromboembolism, two with arterial thrombosis (Table 1). Two of them were diagnosed in the postoperative period, but one of them was suspected to have the event before the surgery. Remaining one of the three patients was diagnosed with recurrent pulmonary thromboembolism both before and after surgery for CS.

**Table 1** Location and time of thromboembolism in our patient population.

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Aetiology of CS</th>
<th>Vessel</th>
<th>Thromboembolic event</th>
<th>Time of diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 45-F</td>
<td>Pituitary adenoma</td>
<td>Venous</td>
<td>DVT of lower extremity</td>
<td>Preoperative period</td>
</tr>
<tr>
<td>2 40-M</td>
<td>Pituitary adenoma</td>
<td>Arterial</td>
<td>Subacute thrombosis of external iliac artery</td>
<td>- After 4 months</td>
</tr>
<tr>
<td>3 42-M</td>
<td>Ectopic</td>
<td>Arterial</td>
<td>Fatal PTE</td>
<td>Before 9 months After 2 weeks</td>
</tr>
</tbody>
</table>

DVT, deep venous thrombosis; PTE, pulmonary thromboembolism.

**Discussion**

Thromboembolism may occur before and after surgery in CS. It generally occurs in the first year, especially in the first 3 months following surgery. It may be venous or arterial in origin. Thus, thrombophylaxis should be administered to patients with active CS before and after the surgery for 6 months.

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**EP22**

Short Synacthen testing: are we referring appropriately and over diagnosing adrenal insufficiency?

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**Background**

A previous short Synacthen test (SST) audit in our hospital (2012) showed 70% of initial SST tests were normal with 9% inappropriate requests. A new pro forma was devised whereby one of four criteria (specific symptoms, medications, previous diagnosis, and physical findings) had to be satisfied to be able to undergo a SST. Additionally, we noticed that a number of patients were probably being over-diagnosed with adrenal insufficiency (AI) based on a single 30 min cortisol estimation following SST.

**Aims**

To evaluate if this new pro forma helped reduce inappropriate referrals for SST and whether the added value of 60 min cortisol (rather than only 30 min) helped minimise overdiagnosis of AI.

**Method**

The results of this new proforma and a full SST incorporating both 30 and 60 min cortisol following SST were collected and analysed between Sept and Nov 2014.

Results

All 27 requests (100%) for SST were appropriate. 63% (1/727) of patients had an abnormal result at 30 min and 44% (1/272) at 60 min. 12 patients (44%) had both abnormal 30 and 60 min cortisol results (five on steroids, five asymptomatic, four with pituitary pathology, three hypopituitarism, and one each with hypotension, T1DM and and new pigmentation). 18% (5/27) had an abnormal result at 30 min but a normal result at 60 min. 4/6 patients referred with hypotension/hypopituitarism had an abnormal SST result. 7/17 patients who satisfied only the ‘symptoms’ criteria had a normal SST result whereas 9/5 patients who satisfied the ‘symptoms’ criteria and at least one other criteria had a normal result.

Conclusion

The new pro forma has made the referral system more effective. Nearly a fifth of over diagnosis of AI can be prevented by routinely measuring serum cortisol at 60 min. By selecting symptomatic patients who satisfied at least one other criteria will also further help minimise unnecessary SSTs.

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EP25

Problems in ACTH–ectopic syndrome diagnostics in clinical practice
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Introduction
Cushing’s syndrome describes symptoms associated with prolonged exposure to inappropriately high levels of cortisol. It may be increased as a result of high ACTH production in the pituitary gland or from tumours outside pituitary-adrenal system.

Case report
Patient 34 years old was hospitalised with complaints of muscle weakness, shooting-pain in thoracic, lumbar spine, decreased height, amenorrhea, arterial hypertension and change in appearance at September 2009. The first symptom of disease was elevated blood pressure at 2007. Patient marked appearance of red shooting-pain in thoracic, lumbar spine, decreased height, amenorrhea, arterial hypertension, and weight loss.

Conclusion
Although there was no difference in cortisol exposure, there was less cortisone exposure in patients than controls, possibly due to the pharmacological effect of hydrocortisone on the 11-β-hydroxysteroid dehydrogenase enzymes. Lack of cortisone exposure and less metabolism of cortisol in patients with AD may predispose to metabolic consequences.

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EP26

Primary adrenal lymphoma: case report
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Introduction
Malignancy is an uncommon cause of adrenal incidentaloma in patients without a known diagnosis of cancer. The actual frequency of primary adrenal carcinoma in patient with adrenal incidentaloma is ~2–5%; another 0.7–2.5% have nonadrenal metastases to the adrenal gland. The presence of a nonadrenal primary tumour is exceptional and has been scarcely reported in medical literature.

Case report
We present a case of 71-year-old male who presented with fatigue, anorexia, weight loss, and hypotension. Initial laboratory evaluation didn’t reveal any anormal result. Computed tomography (CT) scans of the abdomen and pelvis demonstrated large bilateral adrenal masses (the right adrenal gland measured 15.8×6.4×7 cm and the left adrenal gland measured 11.6×5.2×5.6 cm). The masses were nonfunctional according to hormone test results (cortisol of 270 mmol/l, ACTH level of 92.18 pmol/l, 24 h urinary level of normetanephrine 425 µg/day, and metanephrine 148 µg/day). The laboratory test showed adrenal insufficiency (plasma cortisol of 267.62 nmol/l, cortisol failed to increase during the ACTH stimulation test (267.62–226.23 nmol/l) and ACTH was elevated (79.03 pmol/l). A CT-guided core needle biopsy of the left adrenal mass was performed and revealed diffuse large B-cell lymphoma. Bone marrow biopsy was negative for lymphomatous involvement. An F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) scan showed intense FDG accumulation in both adrenal glands (SUV 24.6), there was no abnormal FDG uptake in the rest of the body.

Conclusions
Primary adrenal lymphoma is a very rare extranodal lymphoma, generally occurring among patients of advanced age (mean: 68 years) and dominantly in males. The most frequently histological type is diffuse large B-cell lymphoma and is usually bilateral. Prognosis is poor. Treatment consist in chemotherapy regimen (the most common regimen is CHOP (rituximab, cyclophosphamide, vincristine, and prednisone)) and in some cases treatment with surgery and radiotherapy is necessary.

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EP27

Cushing’s syndrome and diabetes
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Introduction
Cortisol has numerous actions on glucose metabolism and insulin action which explain the frequency of glucose abnormalities in Cushing’s syndrome (CS). The aim of our work was to assess the prevalence and characteristics of diabetes in CS.

Material and methods
This is a retrospective study concerning 51 CS (44F/7M) in whom we looked for the presence of diabetes either by fasting glycaemia or 75 g oral glucose tolerance test. Thereafter, we looked for the characteristics of diabetes in CS. Material and methods

Conclusions
55% of patients have diabetes. Among diabetic patients, 39% have high blood pressure and 42% have a family background of diabetes. 40% of diabetics were treated with oral treatment, 25% with insulin and 35% were on life style therapy. Mean age was 31.92 ± 10.26 years; it was 31.47 ± 10.54 years in patients with diabetes vs 32.45 ± 10.04 years in patients without diabetes. Mean BMI was 30.17 ± 7.33 kg/m²; it was 31.30 ± 7.77 kg/m² in patients with diabetes vs 31.89 ± 6.47 kg/m² in patients without diabetes. Diabetic retinopathy was present in 10% and diabetic neuropathy in 5%. After treatment of CS diabetes resolved in 40% and persisted in 60%.
Conclusion
Diabetes mellitus is frequent in cortisol excess states, the high frequency of diabetes in our study may be explained by preexistent undiagnosed diabetes as diabetes persisted in 60% after resolution of CS.

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EP30
Asymmetric dimethylarginine level and markers of atherosclerosis in Cushing’s syndrome
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Objective
Cushing’s syndrome (CS) is related to diabetes mellitus, dyslipidaemia, hypertension, and obesity, which lead to cardiovascular disease (CVD). CVD is the major cause of mortality and morbidity in CS. The aim of our study was to investigate CVD risk markers, such as asymmetric dimethylarginine (ADMA), lipoprotein-associated phospholipase A2 (Lp-PLA2), highly sensitive C-reactive protein (hsCRP), homocysteine, lipid levels, ankle-brachial index (ABI), and carotid intima–media thickness (CIMT) in CS.

Results
Plasma ADMA levels were significantly lower in CS compared to the control group (P = 0.013). Total cholesterol, LDL cholesterol, HDL cholesterol, apo A1, and apo B levels were higher in patients with CS than the control group (P < 0.05). We did not find any statistically significant difference in hsCRP, Lp-PLA2, and homocysteine levels, CIMT and ABI measurements between CS and control groups (P > 0.05).

Conclusion
Our results suggest that CVD in CS may occur primarily due to comorbid diseases with CS. We found that ADMA levels were lower in CS than co-morbid diseases matched control group, which should be further investigated.

Disclosure
This project was supported by IMSED (Internal Medicine Postgraduate Education Association).

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EP31
A case of aldosterone-secreting giant adrenal carcinoma: a case report
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Introduction
Primary aldosteronism is presented with signs of hypertension and hypokalaemia classically, however, primary adrenal carcinoma is very rare condition. We aimed to present a patient with a metastatic adrenal carcinoma after the primary diagnosis of hyperaldosteronism.

Case report
A 46 years old male patient was referred to our hospital with weakness, dry mouth and weight loss. He had last weight as 31 pounds during last 3 months. Physical examination revealed diffuse cratches in lungs. The others system examination was found normal within any organomegaly or lymphadenopathy. Arterial tension was measured 170/100 mmHg, serum sodium 140 mEq/dL, potassium 1.9 mEq/dL at admission. Differential diagnosis was planned on uncontrolled hypertension and persistent hypokalaemia with elevated aldosterone levels and low renin levels as 735 ng/dl (3–28 ng/dl) and 0.57 ng/ml per h (0.65–5 ng/ml per h) respectively. After potassium replacement therapy, potassium was 3.1 mEq/dL. Doxazosin 8 mg/day with spironolactone 100 mg/day was started. Supression was established with 1 mg dexamethasone in cortisol level. In thorax–abdominal CT was showed bilateral diffuse nodules (biggest was nearly ~2.5 cm) in lungs were consisted with metastatic cancer. A giant mass with 12 cm diameter in suprarenal region, which involves liver partially, consisted with adrenal gland tumour was determined. The military tuberculosis ruled out by bronchoscopy. Metastatic multiple hyper-metabolic lesions in lungs and hyper-metabolic mass in surrenal region were detected in positron emission tomography. Fine needle aspiration biopsy was performed from right surrenal

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mass with CT scan. Pathology revealed adrenocortical carcinoma. Chemotherapy (mitotane) was the chosen treatment because of the distant metastases. Patient died during the chemotherapy.

Conclusions
Primary adrenal carcinoma is very rare with annual incidence of one per one million populations. Less than 1% of all secretes aldosterone. Also clinicians should be aware that primary hyperaldosteronism could occur in the context of adrenocortical carcinoma.

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EP32
The incidence and characteristics of adrenal insufficiency among patients with suspicious symptoms in general hospital in Korea Namkeong Kim, MiKyung Kim, Nanhee Cho, YeYeon Lee & Hyesoon Kim Keimyung Medical School, Daegu, Republic of Korea.

Objective
Adrenal insufficiency is the clinical manifestation of deficient production or action of glucocorticoids, with or without mineralcorticoids deficiency and adrenal androgens. The mortality of untreated adrenal insufficiency reaches up to 80% in 2 years. Moreover, the symptom is non-specific like malaise, dizziness. Therefore, history taking, prompt diagnosis and management are more important. The diagnostic investigation, although well established, can be challenging, especially in patients with secondary or tertiary adrenal insufficiency. However, information about the prevalence and characteristics of adrenal insufficiency in Korea is lack. Therefore, we reviewed the characteristic of patients of adrenal insufficiency.

Methods
We reviewed medical records of patients who visited Keimyung University Dongsan Medical Center for 4 months and conducted a test such as rapid ACTH stimulation test and insulin tolerance test.

Results
In 267 participants enrolled, most common reason (38.9%) to conduct a test was that patients complained suspicious symptoms related with adrenal insufficiency and the second reason (29.6%) was for diagnosis the cause of hyponatraemia. Among them, 37.4% patients was diagnosed as adrenal insufficiency. 70% was female and mean age was 65.23 years old. Basal cortisol level was 3.93 ± 3.81 and it was significantly lower than normal patients (P = 0.000). Common symptoms are anorexia, nausea, dehydration, and arthralgia. 67% patients had history of steroid medication and 53% of patients took steroid within 3 months.

Conclusion
A lot of patients who diagnosed adrenal insufficiency are related with steroid medication. History taking about long-term use of steroid is necessary for early detection. Basal cortisol level could not be diagnosis but provide an useful clue for diagnosis of adrenal insufficiency. In addition, when we use steroid, we are more cautious about development adrenal insufficiency. We need further study to evaluate the prevalence and characteristics in a large population.

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EP33
A case of Addison’s disease: high clinical suspicion should guide diagnosis and caution should be used when reviewing initial laboratory investigations
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A 69-year-old lady with a history of autoimmune diabetes mellitus and primary autoimmune hypothyroidism presented to the Specialist Diabetes Clinic with a significant inexplicable variation in her capillary blood glucose. She had been undergoing investigations with the gastroenterologists for nausea, vomiting, and weight loss. Despite extensive investigations including: oesophageal–gastro-duodenoscopy, CT–thorax, abdomen, pelvis scanning, and gastric emptying studies no cause for her symptoms had been found. Her drug therapy included ranitidine, omeprazole, metformin, levothyroxine, folic acid, simvastatin, lantus, and novarapid. Given her clinical presentation and autoimmune diagnoses, metformin was stopped and she was investigated for adrenal insufficiency. Her basal serum cortisol was 410 nmol/l (normal range >400 nmol/l). Her short Synacthen test results were 421 nmol/l at 30 min and 433 nmol/l at 60 min. Basal ACTH 1100 ng/l (normal range 5–46), plasma renin 28 nmol/l per h (normal range 0.5–3.1), and plasma aldosterone 110 pmol/l (normal range 100–800). Anti-adrenal antibody titre was positive at 1:10 dilution.

Discussion
Baseline serum cortisol level was perceived to be adequate; however response to ACTH was stunted. The ACTH, aldosterone, and renin levels together with positive anti-adrenal antibody titre are consistent with a diagnosis of primary autoimmune adrenal insufficiency (Addison’s disease). She was immediately started on hydrocortisone replacement with explanation about steroid sick day rules, mineralocorticoid was added and she was reviewed in clinic 3 weeks later. Her glycaemic profile improved, hypoglycaemic episodes were abolished and gastrointestinal symptoms completely resolved. This case highlights the importance of retaining a high degree of clinical of suspicion in diagnosing adrenal insufficiency despite a ‘normal’ basal cortisol and how ACTH, aldosterone, renin, and anti-adrenal antibody testing may aid diagnosis in such cases.

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EP34
Selective adrenal venous sampling is not always useful in primary aldosteronism
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Adrenal venous sampling (AVS) is regarded as the gold-standard for the study of lateralisation of primary aldosteronism (PA) after its biochemical diagnosis. After catheterisation of both adrenal veins, confirmed by ratio of cortisol concentration in each adrenal vein and peripheral vein (selectivity index (SI)), lateralization is accepted if aldosterone/cortisol (A/C) ratio between both adrenal veins is over 3–4 (lateralization index (LI)), particularly if non-dominant vein has A/C level lower than peripheral vein. We present two cases of PA with selective AVS, but puzzling results about lateralisation: case 1 – woman (52 years), severe hypertension for the last 2 years, with elevated ratio aldosterone/plasminic renin activity (RAR) and urinary aldosterone of 16.4 μg/24 h with hypernatriuria (340 mEq/24 h). First sample showed right SI of 44.3 and left SI of 12.2, and suggested bilateral production (LI: 1:12), with both adrenal A/C levels higher than peripheral vein. Second sample, 5 min later, showed right SI of 18.9 and left SI of 10.3, but indicated right lateralisation (LI: 3.2), coincident with adrenal tumour in CT, with A/C ratio in left vein lower than peripheral A/C ratio. Case 2 – woman (52 years), severe hypertension, only one selective sample in AVS (right SI: 10.83 and left SI: 15.32). A/C ratio in both veins lower than peripheral vein (18.2 and 8.5 vs 71.9). Normal CT scan. These two cases illustrate potential inaccuracies of AVS. These probably are due to superselective canalisation of adrenal veins, not draining venous effluent of the tumour producing aldosterone excess. In both cases, right SI were very high. These high ratios have been proposed as suggestive of very selective sampling, collecting blood of suppressed adrenal tissue, but not from the adenoma. Other possibility in the second case is anomalous drainage of pathologic tissue, by accessories veins, not canulated in AVS.

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EP35
The safety of steroid replacement and patient’s knowledge
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A 69-year-old lady with a history of autoimmune diabetes mellitus and primary autoimmune hypothyroidism presented to the Specialist Diabetes Clinic with a significant inexplicable variation in her capillary blood glucose. She had been undergoing investigations with the gastroenterologists for nausea, vomiting, and weight loss. Despite extensive investigations including: oesophageal–gastro-duodenoscopy, CT–thorax, abdomen, pelvis scanning, and gastric emptying studies no cause for her symptoms had been found. Her drug therapy included ranitidine, omeprazole, metformin, levothyroxine, folic acid, simvastatin, lantus, and novarapid. Given her clinical presentation and autoimmune diagnoses, metformin was stopped and she was investigated for adrenal insufficiency. Her basal serum cortisol was 410 nmol/l (normal range >400 nmol/l). Her short Synacthen test results were 421 nmol/l at 30 min and 433 nmol/l at 60 min. Basal ACTH 1100 ng/l (normal range 5–46), plasma renin 28 nmol/l per h (normal range 0.5–3.1), and plasma aldosterone 110 pmol/l (normal range 100–800). Anti-adrenal antibody titre was positive at 1:10 dilution.

Discussion
Baseline serum cortisol level was perceived to be adequate; however response to ACTH was stunted. The ACTH, aldosterone, and renin levels together with positive anti-adrenal antibody titre are consistent with a diagnosis of primary autoimmune adrenal insufficiency (Addison’s disease). She was immediately started on hydrocortisone replacement with explanation about steroid sick day rules, mineralocorticoid was added and she was reviewed in clinic 3 weeks later. Her glycaemic profile improved, hypoglycaemic episodes were abolished and gastrointestinal symptoms completely resolved. This case highlights the importance of retaining a high degree of clinical of suspicion in diagnosing adrenal insufficiency despite a ‘normal’ basal cortisol and how ACTH, aldosterone, renin, and anti-adrenal antibody testing may aid diagnosis in such cases.

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**EP36**

**Pituitary macroadenoma with adrenocortical hypersecretion as the initial presentation of compensated adrenocortical failure**

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Long-standing primary failure of pituitary-dependent endocrine glands may induce pituitary hyperplasia and adenoma both related to duration and severity of peripheral gland insufficiency, although the formation of an adenoma is rare. We report the case of an elderly man with pituitary macroadenoma but compensated adrenocortical failure. A 70-year-old man referred our centre in 2013 for headache and horizontal diplopia. MRI revealed pituitary macroadenoma (1.9 × 1.1 × 2.2 cm) with suprasellar extension, invasion of cavernous sinus, very close to the optic chiasm, localised T1 weighted-hyperintensity area suggestive of bleeding. Hormonal evaluation showed central hypothyroidism, hypogonadotropic hypogonadism, normal PRL, and GH/GF1 serum levels, ACTH hypersecretion (fourfold above normal upper limit) with cortisol basal serum level at 21.2 µg/dl; renin and aldosterone serum levels were in the normal range; antibodies to adrenal cortex were negative, while those 21OH-Ab and very-long-chain fatty acid unexpectedly could not sampled; ANA-AMA-ADNA-ASMA-APCA, antiphospholipid Ab and TgAb-TPOAb were negative. Adrenal glands appeared normal at CT scan. Medical history was negative for tuberculosis. Weight loss, hypotension, dehydratation, hyperpygmentation, fever, abdominal pain, as well as hypertension, hypo- or hyperkaliaemia, hypo- or hypercalcaemia were not present; type 2 diabetes mellitus was diagnosed. Transphenoidal endoscopic excision was performed; the specimen was identified as adenoma at microscopical examination and immunocytochemical analysis showed diffuse immunoreactivity for ACTH, absent immunoreactivity for FSH, PRL, TSH, and GH; Kt67 <3% with p53 not expressed. In conclusion, this case shows that the formation of a pituitary adenoma is also possible in the forms yet compensated adrenal insufficiency; likely duration of adrenal failure, rather than the severity, may led a major role in the formation of the pituitary adenoma.

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**EP37**

**Pregnancy-induced Cushing’s syndrome**

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Cushing’s syndrome (CS) during pregnancy is a rare metabolic condition with only a few cases reported in the literature. Misdiagnosis of CS is common because of the overlapping features of fatigue, weight gain, striae, and emotional changes that occur during normal pregnancy. The clinical presentation together with laboratory and imaging findings help to make a diagnosis. However, changes in maternal hormones and their binding proteins complicate assessment of the normal level of glucocorticoid hormones during gestation. CS during pregnancy is attributable most frequently to an adrenal adenoma and to a lesser degree to ACTH hypersecretion from a pituitary adenoma. Furthermore aberrant expression of various hormone receptors in the adrenal glands has been suggested to be involved in the pathogenesis of this condition, in particular the LH receptor. We investigated and treated three pregnant women with ACTH-independent CS and an adrenal tumor. After uncomplicated delivery patient 1 underwent in vivo testing for aberrant hormone receptor expression in the adenoma. Cortisol responses were found after administration of LHRH, human chorionic gonadotropin (hCG), TRH, glucagon, vasopressin, and a standard mixed meal. All patients were treated with laparoscopic adrenalectomy, after which signs and symptoms of hypercortisolism partially resolved. Adrenal tumour tissue of patients 1 and 2 showed positive immunohistochemical staining of LH receptors. Considering the cortisol responses to LHRH and hCG, and the development of CS during pregnancy in these patients, it is likely that ACTH-independent hypercortisolism was induced by the pregnancy-associated rise in hCG levels that activated aberrantly expressed LH receptors in the adrenal adenoma. Remarkably adrenal adenomas may simultaneously express multiple aberrant receptors and individual ligands may play a role in the regulation of cortisol production responsible for pregnancy-induced CS.

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**EP38**

**Cardiovascular system abnormalities in patients with Cushing’s syndrome**

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Background

Patients with Cushing’s syndrome (CS) have a lot of complications due to chronic exposure of cortisol. Aim To reveal specific changes of cardiovascular system in patients with CS. Material and methods i) Six patients with CS (five females, one male, 47.1 ± 1.5 years old), duration of CS 3.4 ± 1.2 years; ii) 19 healthy patients (48.1 ± 3.0 years old), and iii) ten patients with ischemic heart disease (IHD) (48.2 ± 3.1 years old). Echocardiography; Holter monitoring (HM) and 24-h ambulatory blood pressure monitoring (ABPM) in bifunctional mode with program assessment of hemodynamic parameters and arterial stiffness (total peripheral vascular resistance (TPVR), index of arterial stiffness, heart rate variability, and circadian index) were assessed.

Results

Arterial hypertension was in all patients with CS. Mean daily BP 176 ± 9/106 ± 6 mmHg. Systolic pressure–time index 67.7 ± 8.7%, diastolic pressure–time index 30.3 ± 10.5%. 24-h rhythms of BP were disturbed in 67%, with prevalence of non-dippers and night-pickers in CS-patients. Strong correlations were found between cortisol levels (0800 and 2300 h) and systolic (SBP) and diastolic (DBP) day and night pressure (for 0800 h cortisol: SBP r=0.75, DBP r=0.8 (P=0.05); and 2300 h cortisol: SBP r=0.9, P=0.01; DBP r=0.95, P=0.05). Index of arterial stiffness was higher in patients with CS in comparison with patients with IHD. TPVR was increased in all patients with CS. Echocardiography: left atrial expansion in 67% of patients (±2.2±1.1 cm), left ventricular hypertrophy (in 50%), diastolic dysfunction (in 67%). Holter: mean heart rate (day 91.6 ± 3.2 and
night 73.5 ± 3.8) were higher in patients with CS than in other groups. 83.3% CS-patients had cardiac rhythm abnormalities that show predominance of activity of sympathetic nervous system.

Conclusion
All tests reveal significant changes in cardiovascular system in patients with CS with great predominance of activity of sympathetic nervous system. Index of arterial stiffness in patients with CS were higher than in patients with IHD, leads to higher risk of serious cardiovascular events in CS.

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EP29
Clinical management of adrenal insufficiency shows significant heterogeneity: data from the EU-AIR study
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Introduction
No consensus guidelines currently exist as to the optimal glucocorticoid regimen in adrenal insufficiency (AI). In clinical practice physicians utilise a number of different glucocorticoids, usually administered in several doses throughout the day.

Methods
The EU-AIR registry is a European multinational, multicentre, prospective, observational study sponsored by Shire inclusive of all patients with AI irrespective of aetiology. We analysed the baseline data of patients with primary (PAI) and secondary AI (SAI), excluding patients with CAH, to gain insight into AI current clinical management.

Results
As of 5th November 2014, 946 patients with AI (54.6 ± 16.4 years, 510 (53.9%) F; BMI 28.0 ± 5.5 kg/m², 310 (32.8%) PAI) were enrolled in to the study. Overall 91.8% of patients were receiving hydrocortisone (HC) as preferred glucocorticoid replacement. 6.8% prednisolone, 1.6% cortisone acetate, and 0.1% dexamethasone. For patients receiving HC, daily doses ranged from 5 to >45 mg. Most patients received 20–<25 mg (44.9%), with 24.3 and 16.0% receiving 15–<20 and 25–<30 mg respectively. 15.0% of patients were receiving HC doses ≥30 mg. Patients with PAI and SAI were receiving average HC doses of 23.3 and 19.3 mg respectively. HC was taken OD, BID, TID, and QID in 67.5, 52.1, 43.9, and 1.8% respectively. Patients with PAI were more likely to be receiving HC TID compared with those with SAI (56.9% vs 37.6%), who received their HC most frequently as a BID dosage (42.0% vs 56.9%). For patients receiving prednisolone daily doses ranged from <2 to >7.5 mg, with the majority (65.6%) receiving 5–<6 mg/day. A daily dose ≥6 mg was taken by 21.8%. Prednisolone was taken OD, BID, and TID in 73.4, 29.7, and 1.6% respectively.

Conclusions
We have demonstrated significant heterogeneity in the current management of AI in type of glucocorticoid, dosage, and frequency of administration. This likely reflects individualisation of regimes in the absence of robust data supportive of the optimal regimen for long-term outcomes.

Disclosure
This work was supported by Shire International GmbH.

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EP40
Postural orthostatic tachycardia syndrome unmasked by successful treatment of primary aldosteronism
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A 50-year-old woman was referred with a history of chronic, symptomatic hypokalaemia. She also had hypertension. There was no history of diarrhoea, increased bowel motions, vomiting, or laxatives/diuretic use. She was not diabetic and she did not have menopausal symptoms. Her mother had seven strokes and myocardial infarction. On examination weight was 69.9 kg, height 1.65 m, BP 163/99, pulse 70, heart sounds normal, and examination of the abdomen was unremarkable. ECG was normal. Despite taking potassium supplements, repeat blood tests showed sodium 148 mmol/l, potassium 3.3 mmol/l, magnesium 0.87, creatinine 56, and eGFR > 90. Spot urine potassium 25 mmol/l. Primary aldosteronism was suspected. Her renin was undetectable (<1.1 ng/l) and serum aldosterone 772 pmol/l. Saline suppression test showed non-suppressible aldosterone levels. Glucocorticoid-remediable aldosteronism was excluded. MRI failed to show a adrenal lesion. Adrenal vein sampling however confirmed a unilateral, right sided adrenal source for the aldosterone excess and she underwent successful right adrenalectomy. Histology was supportive of the diagnosis. Shortly after the operation she started to experience significant postural dizziness. It was initially thought that this was due to relative suppression of aldosterone secretion by the contralateral gland and so fludrocortisone was started. A short Synacthen test excluded adrenal deficiency. She required increasing doses of fludrocortisone but despite this remained symptomatic. Additionally she experienced headaches, fatigue, cold intolerance, and breathlessness. Therefore a neurocardiogenic process was suspected and she was referred to cardiology. Tilt table test showed her heart rate gradually rose to 138 b.p.m. This was thought to be consistent with a POTS type response. Thus our patient had confirmed primary aldosteronism due to a adrenal adenoma, removal of which helped to unmask POTS. We hypothesise that the excess mineralocorticoid activity from the adenoma hyper secreting aldosterone helped to mask the neurocardiogenic process.

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EP41
Effect of stress-dosed hydrocortisone on physical capacity in patients with Addison’s disease
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The current conventional glucocorticoid (GC) replacement therapy in primary adrenal insufficiency (Addison’s disease) and congenital adrenal hyperplasia (CAH) renders the cortisol levels unphysiological, resulting in very high levels alternating with almost undetectable levels of cortisol over the day. This reduces not merely the patient’s quality of life but increases the patient’s morbidity and mortality. The HPA axis is characterised by a dynamic circadian variation of cortisol with highest circulating levels in the early morning and a nadir late in the evening. The current therapeutic approach does not restore the circadian rhythm of cortisol. Recently replacement by continuous subcutaneous hydrocortisone infusion (CSHI) has been shown to mimic the circadian cortisol rhythm (Oksnes et al. 2014). CSHI treatment requires proper patient education and close monitoring during the first week of treatment until the correct dosage of hydrocortisone is defined. The starting dose is calculated according to body surface area and divided into four dosing intervals per day, corresponding with the circadian rhythm of cortisol. During the first day, the patient may report clinical signs of under-treatment; thus it is essential that the patient is thoroughly informed, and has the possibility to contact the physician directly if needed. The cortisol dosage should be double-checked in one week with serum cortisol, ACTH, cortisol saliva profile, and (possibly) 24 h urine collection, allowing for dose adjustment. In case of any illness the patient has to switch to the conventional tablet treatment and increase the dose of hydrocortisone according to the recommendation.

Disclosure
The work was supported by grant of Helse-Bergen Norway.

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**EP42**

Phenotypic characteristics of bilateral adrenal masses: about 34 cases
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Introduction
Bilateral adrenal tumours are rare and account for 10–15% of adrenal lesions. They can be infectious, inflammatory, tumour, hémorragiques, and genetic. The clinical and imaging used to guide diagnosis.

Aim
Assess clinical, etiologic, and therapeutic characteristics of bilateral adrenal masses.

Population and methodology
This is a retrospective study of the records of patients with bilateral adrenal masses collected over 26 years. All patients have benefited from a biological exploration (specific and non-specific) and oriented radiological investigation.

Results
34 patients were identified. The mean age at diagnosis was 45 ± 0.4 years. Sex ratio was 24 men/10 women. Diagnostic circumstances were: a chance discovery 11.8%, exploration of congenital adrenal hyperplasia (n: 44.11%), the staging of thyroid cancer: 17.64%, the exploration of a failure adrenal: 2.94%, 23.51% adrenergic signs. The etiological exploration revealed a bilateral pheochromocytoma 10 (29.4%), nodular adrenal hyperplasia 15 (44.1%), and adrenal tuberculosis 1 (2.94%). The surgical was reported in 41.17% (all cases of pheochromocytoma, nodular adrenal hyperplasia: 3, suspicious adrenal masses of primitive non-Hodgkin lymphomenn: 1). The intervention was recused in other cases of adrenal metastases. Monitoring was instituted in other cases.

Discussion and conclusion
Bilateral adrenal masses are quite particular entity because of their rarity, their aetiologies and treatment. They must be characterised to be treated effectively. The improvement of radiological techniques and therapeutic modalities have enhanced their management.

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**EP44**

Adrenal inclusions in congenital adrenal hyperplasia: clinical and progressive characteristics
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Introduction
Intra-testicular adrenal inclusions (ISIT) are benign tumors made of ectopic adrenal cortex tissue hyper stimulated by ACTH in excess. All pathologies causing a rise ACTH levels may be associated with adrenal inclusions. They are found mainly in patients with congenital adrenal hyperplasia (CAH) of untreated or poorly treated.

Objective
Search the frequency of ISIT in CAH and clarify clinical and progressive characteristics.

Materials and methods
Forty patients with CAH responsible adrenal insufficiency (35 in 21 and one in five hydroxylase) underwent testicular echo-Doppler in search of ISIT. The volume of each testicle, the presence of ISIT, their size, echogenicity, and vascularity at diagnosis and during follow up.

Results
Adrenal inclusions were found in ten patients (25%). They were asymptomatic and bilateral in all case. Doppler ultrasound was suggestive in all patients (hilar localisation, mitigating but not calcified appearance, vascular architecture preserved). Partial regression after glucocorticoid treatment was noted in 95% of cases. In two cases the adrenal inclusion continued to grow requiring orchidectomy. Histological study was in favour of a Leydig cell tumours.

Discussion and conclusion
ISIT are common in CAH (between 27 and 94%). Related to chronic stimulation by ACTH, they often reflect an insufficient suppressive treatment with glucocorticoid. The Doppler allows the characterisation. They must be systematically sought and monitored. They usually regress or stabilise with replacement glucocorticoid treatment. Sometimes they can grow, while raising the problem of the histological nature and risk of subfertility related to the mass effect of the ISIT and toxic effects of adrenal steroids and hpgonadotropic hypogonadism.

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**EP43**

Impact of congenital adrenal hyperplasia and glucocorticoid treatment on the final size and gonadal function
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Introduction
Congenital adrenal hyperplasia (CAH) are genetic diseases with a deficit of one of the enzymes of steroidsogenesis (21 hydroxylase OH, 90%). The consequences of the adrenal hyperandrogenism that results are observed when the treatment is not undertaken precociously.

Aim
To study the impact of CAH and or treatment by glucocorticoids on the final size and gonadal function in girls.

Materials and methods
25 patients with CAH by 21-hydroxylase deficiency (n = 25) or 11β-hydroxylase (n = 3) with completed puberty were studied to assess the impact of affection and or glucocorticoid treatment on final height, pubertal development, and gonadal function in girls. Impact of congenital adrenal hyperplasia and glucocorticoid treatment on the final size and gonadal function.

Results
The mean age at diagnosis and initiation of treatment was 5 ± 2.4 years old (3–9). Bilateral final height was 150 ± 1.2 cm for girls (n = 18) and 158 ± 2 cm for boys (n = 7). 20% of patients have early puberty. In the remaining cases, delayed puberty was observed with a mean age of 14 ± 0.1 and 17 ± 1.2 years for onset of puberty and menarche in girls; 15 ± 1.4 years for boys. All girls had polycystic ovarian disease. 70% of patients had a persistent hyperandrogenism. 50% of patients were tightly controlled, 25% underdosed, and 25% overdosed.

Discussion and conclusion
Delayed diagnosis and poor compliance in our patients have resulted in a significant impact on growth in stature, pubertal development, and gonadal function. The introduction of routine neonatal screening for CAH in our country and more efficace care of pathology will improve the functional prognosis of patients.

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**EP45**

X-linked adrenal hypoplasia congenita with a novel DAX1 missense mutation
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Introduction
X-linked adrenal hypoplasia congenita (AHC) is a rare developmental disorder of the adrenal cortex. Adrenal insufficiency typically begins in infancy or in childhood. A few individuals present adrenal insufficiency in adulthood. Case report
A 21-year-old man visited our endocrine out-patient clinic due to underdeveloped secondary sexual characteristics, which was found at physical examination for military service. Physical examination revealed small bilateral testes, sparse pubic, axillary hair, and a large arm span-to-height ratio. Besides, pigmentation in mouth, on palmar creases and joints were noted. Endocrine function evaluation showed high ACTH (> 1250 pg/ml), low cortisol (5.37 µg/dl), low testosterone (0.541 ng/ml) with low FSH (4.79 mU/ml), and low LH (2.77 mU/ml). Peak LH level was 16.4 mU/ml after LHRH stimulation, but response of FSH, LH, and testosterone to clomiphene was impaired. Thyroid function, HbA1c and serum electrolyte, plasma renin activity, and aldosterone levels were normal. Abdominal computed tomography scan revealed bilateral small adrenal glands. Brain MRI revealed no lesion at pituitary gland or hypothalamus. Adrenal hypoplasia congenital was suspected due to combined primary adrenal insufficiency and hypogonadotropic hypogonadism. Genetic study revealed a missense mutation (c.849G>C) in the DAX-1 gene (dosage-sensitive sex reversal adrenal hypoplasia congenita, critical region on the X chromosome gene-1), which was transmitted from his mother.

Conclusion
DAX-1 gene deletions or mutations have been reported to be responsible for AHC. We report a case of AHC with adult-onset adrenal insufficiency, hypogonadotropic hypogonadism, and a novel missense mutation in the DAX-1 gene.

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EP46
Adrenal insufficiency during prednisolone treatment: need for cortisol replacement strategies in patients on long-term low-dose glucocorticoid treatment?
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Background
Patients on long-term glucocorticoid treatment are at risk of adrenal insufficiency during glucocorticoid treatment. The side effect can occur during glucocorticoid treatment if there is a mismatch between glucocorticoid requirements and production/intake. High-dose glucocorticoid treatment is often sufficient to overcome most stressful situations. A low-dose of 5 mg prednisolone/day is however, equivalent to 20 mg hydrocortisone, a dose often used as basal glucocorticoid replacement in adrenal insufficiency. Contrary to patients in replacement therapy for adrenal insufficiency, patients treated with long-term low-dose glucocorticoids for various reasons are often not instructed in self-administration of supplemental doses in stressful situations.

Objective
We aimed to assess the prevalence of adrenal insufficiency in patients treated with 5 mg prednisolone/day.

Subjects and measures
As part of a larger study, 37 patients with rheumatoid arthritis (26 women, aged 36–85 years) treated with 5 mg prednisolone/day for at least 6 months (mean 108, range 6–336 months) had a 250 μg Synachten test performed, after mean prednisolone pause of 47 h (range 36–96 h). P-cortisol was measured before and 30 min after Synachten injection. Cut-off for normal adrenal function was 30 min P-cortisol > 500 nmol/l as this is validated for our local cortisol assay. As a cut-off of 550 nmol/l is often used these data are also shown.

Results
Of the 37 patients 11 (30%) had an insufficient adrenal response to the Synachten test. Using cut-off of 550 nmol/l 16/37 (43%) had adrenal insufficiency.

Conclusion
We found adrenal insufficiency in approximately one third of patients treated with 5 mg prednisolone/day. Since prednisolone treatment is often sustained for years in these patients, adrenal suppression is likely equally prolonged. Our findings raise the question whether a Synachten test should be routinely performed in patients on long-term low-dose glucocorticoid treatment and insufficient patients handled with the same cortisol replacement strategies as other patients with verified adrenal insufficiency.

Disclosure
This study was supported by the Eva Maduras Foundation.

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EP47
A challenging case of paraneoplastic Cushing’s syndrome
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Introduction
Paraneoplastic Cushing’s syndrome (CS) represents 5–10% of all CS and has a severe prognosis due to severe metabolic imbalance, denutrition, associated infections, and progression of tumoral underlying pathology. A 67 years old woman presented with mental confusion, progressive weight loss, severe oedema and hypokalaemia, without typical features of Cushing on hyperpigmentation. Investigations revealed paraneoplastic Cushing’s with ACTH 82.5 pg/ml, cortisol levels more than 63 μg/dl, probably produced by pulmonary tumour. Patient associated also empty sella syndrome with TSH and gonadotrophic insufficiency, left breast tumour, Helicobacter pylori gastritis, polinodular goitre, denutrition, and hepatic dysfunction. 99mTc tetrotyd scintigraphy was negative for pulmonary tumor, showing uptake in both adrenals and brain. Patient needed 1200 mg/day ketoconazole and 200 mg/day of mifepristone in order to obtain normal cortisol levels and metabolic parameters. Owing to pulmonary sepsis and hepatic dysfunction we choose left adrenalectomy as first intervention, allowing reduction of ketoconazole to 600 mg/day and secondary left pulmonary lobe resection. Even if ketoconazole was stopped 1 day prior to adrenalectomy, patient developed adrenal insufficiency, needing noradrenaline support for 1 day and hydrocortisone replacement for 2 days. Histology exam showed benign bronchial carcinoma with ACTH staining and benign hyperplasia of left adrenal. Patient recovered almost completely. Mild hypokalaemia and hyponagaeasemia, even with oral supplementation, sartan therapy and normal levels of cortisol and ACTH persisted after surgery, probably due to severe deficit of intracellular compartment.

Conclusion
This case was difficult due to metabolic challenges, multiple associated pathology, lack of SSTR1 and SSTR3 receptors with negative scan, mild elevation of cromograme A levels despite a typical bronchial carcinoma. Patient’s sister was operated for adrenal adenoma confirmed on histology exam, her daughter had papillary thyroid cancer, but no MEN association was proven in this family.

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EP48
The treatment with ‘dual release’ hydrocortisone (DR-HC) in congenital adrenal hyperplasia: short-term (6 months) and long-term (12 months) follow-up after the switch from conventional glucocorticoids to DR-HC
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In patients with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency, life-long glucocorticoid (GC) treatment is often required to replace cortisol deficiency and to avoid the ACTH-dependent androgen levels increase. However, in these patients, the multiple daily doses required with conventional GCs can cause cortisol overexposure, leading to an increased risk of metabolic syndrome (MS), an impaired quality of life (QoL), and poor treatment compliance (TC). The current study aimed at investigating the impact of the switch from twice or thrice daily conventional GCs to once daily ‘dual release’ hydrocortisone (DR-HC) on metabolic and hormonal profile, QoL, depression status (DS), and TC in a cohort of patients with CAH. Twenty-three CAH patients (16F, 7M, 20–38 years), treated with HC (10–40 mg/day) or prednisone (6.25–12.5 mg/day) for at least 12 months, switched to DR-HC (10–40 mg/day) entered the study and were evaluated before and after 6–12 months of DR-HC. Metabolic and hormonal parameters were measured using routine assays and the MS was evaluated according with IDF criteria. QoL, DS, and TC were assessed using AddQoL Questionnaire, Beck Depression Inventory II, and Mirtsysy 8-items medication Adherence Questionnaire respectively. The change in metabolic and hormonal parameters in the same cohort of patients along the year between baseline and 12 months after the switch, while patients stably performed conventional GCs, was used as control. At 6-month follow-up, fasting plasma glucose (P = 0.003) was significantly reduced, whereas at 12-month follow-up HDL (P = 0.000) and LDL-cholesterol levels (P = 0.024) were significantly improved as compared with baseline. A clear diagnosis of MS was performed in one patient at baseline, but this patient displayed no criteria for this diagnosis after 6 and 12 months. No significant change in morning plasma ACTH, UFC, and serum aldosterone, 17-OH progesterone, testosterone, DHEA-S, and androstenedione levels were observed and no clinical worsening of symptoms and signs related to hyperandrogenism were reported. Excluding from the analysis the four patients treated with prednisone at baseline, a significant increase in morning serum cortisol levels was registered after 6 months (P = 0.016) but it was not confirmed after 12 months. Despite the unchanged fluorocortisone doses, both in the entire cohort (P = 0.002) and in the subgroup of patients with salt wasting form (P = 0.005) a significant decrease in renin levels was reported at 6 month follow-up, but it was not confirmed at 12-month follow-up. As control, no significant difference was observed in metabolic and hormonal parameters in the same cohort of patients between baseline and 12 months before the switch. Additionally, DS improved both after 6 months (P = 0.04) and 12 months (P = 0.07) whereas TC significantly, progressively, improved after 6 months (P = 0.009) and after 12 months (P = 0.000). In conclusion, the switch from conventional GCs to...
**EP49**
The effect of oxidative stress to cardiovascular risk profile among non-functional adrenal incidentaloma patients

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**Aim**
In this study our aim was to investigate the effects of non-functional adrenal incidentalomas to cardio-metabolic risk factors and endothelial function.

**Materials and methods**
Our study involved 30 patients with non-functional adrenal incidentaloma (patient group), and two control groups without adrenal incidentaloma (control group 1 involved 26 patients have DM and/or HT and control group 2 involved 24 healthy control). Metabolic parameters (fasting blood glucose and lipid profile), hsCRP, oxidative stress parameters such as malondialdehyde (MDA), nitric oxide (NO), nitrotyrosine (3-NTx), and antioxidants parameters such as catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), and melatonin were evaluated in all participants.

**Results**
When we compared the patient and control groups; hsCRP, oxidative stress parameters (MDA, NO, and 3-NTx) were significantly higher in patient group ($P<0.001$) but antioxidant parameters such as melatonin, GPx, and SOD were significantly lower in patient group ($P<0.001$). Cortisol levels after 1 mg dexamethasone suppression test were significantly higher in patient group ($P<0.001$). There was a significant positive correlation between cortisol levels after 1 mg dexamethasone suppression test and hsCRP, MDA, NO, and 3-NTx levels ($P<0.05$) and there was a significant negative correlation between cortisol levels after 1 mg dexamethasone suppression test and melatonin, GPx, and SOD levels ($P<0.001$).

**Conclusion**
Adrenal incidentalomas are usually thought to be benign and asymptomatic lesions. But recent studies reported that autonomic cortisol secretion was higher than expected in incidentalomas and they have increased cardiovascular risk. But it is not clear whether adrenal incidentalomas increase the atherosclerosis and cardio-metabolic risk or this adrenal tumours mostly seen in patients that have cardio-metabolic risks. According to the data obtained from this study; we suggest that the oxidative stress increases markedly in the patients with non-functional adrenal incidentalomas, so this process leads the atherosclerosis eventually. Moreover we showed that non-functional adrenal incidentalomas patients have higher cortisol levels when compared both with healthy controls and patients that have cardiovascular risk factors. Therefore we suggest to consider the factors that mentioned above when evaluating the non-functional adrenal incidentaloma patients.

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**EP50**
Malignant phaeochromocytoma: about seven observations

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**Aim**
Report the observations of seven cases observed in 26 years.

**Materials and methods**
Seven patients with malignant phaeochromocytomas were treated in our department. Three were males and four females and their ages ranged between 17 and 45 years old. The circumstances discoveries were adrenergic signs and severe hypertension in all cases. Hormonal balance showed very high levels of metanephrine: 20±1.4 (16–22) and CT+MIBG showed a large and characteristic adrenal mass: 12.6±1.2 cm (14–9.6). Malignancy was confirmed by the presence of metastasis at diagnosis in five cases and in the developments in the rest of the cases. Evolution was marked a year and a half after on average (after surgery and chemotherapy) by a normalisation of blood pressure, methoxylated derivatives in five patients. Two deaths occurred after the first course of chemotherapy.

**Discussion and conclusion**
Surgery of malignant phaeochromocytoma, even at metastatic stage increases survival. Chemo radiotherapy and MIBG are part of the therapeutic arsenal. The management of these patients requires a multidisciplinary follow up (surgeon, oncologist, endocrinologist, histopathologist, and geneticist).

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**EP51**
Comparison of 17-OH progesterone response to various dose of tetracosactide

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**Aim**
ACTH test is widely accepted as diagnostic tool in suspicion on peripheral as well as on central hypocorticism. The optimal dose of tetracosactide for determination of hypocorticism is still matter of debate. The 250 μg as a standard dose of tetracosactide has been approved for diagnosis of congenital adrenal hyperplasia (CAH) many years ago. Moreover, current limited availability of tetracosactide and its increased financial cost on the market raised the question whether the lower dose of tetracosactide for diagnosis of CAH may be sufficient stimulation.

To compare response of 17-OH progesterone (17-OHP) to various doses of tetracosactide in healthy volunteers.

**Methods**

In ten healthy volunteers (four males, median 42 years) with normal adrenal function (based on clinical and biochemical evaluation) the ACTH tests with i.v. administration of 250 μg (HDST), 10 μg (MDST), and 1 μg (LDST) tetracosactide were performed.

**Results**
Similar response in 17-OHP levels in all three variants of the test was observed. Median 17-OHP levels 30 min after the tetracosactide administration were 6.62, 6.62, and 5.68 nmol/l for HDST, MDST, and LDST respectively. 60 min after the administration the median levels were 6.93, 5.91, and 4.70 nmol/l.

**Conclusion**
Our data support the hypothesis of ACTH test reliability for the diagnosis of CAH in all variants with lower doses of ACTH compared to standard dose. Further confirmation of our observation in patients with known non-classical form of CAH would be appropriate.

**Disclosure**
This work was supported by grant number NT 11277-6 of the IGA MZCR.

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**EP52**
Functional oncocytic adrenocortical tumour: a case report

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**Introduction**
Malignant phaeochromocytomas are rare tumours, developed at the medulla and paraganglia. Their diagnosis is established by the presence of metastases of organs devoid of chromaffin tissue or by the appearance of neoplastic recurrence. They are characterized by a morbidity and mortality due to the effects of uncontrolled and important hypersecretion catécholaminergique and resistance to conventional cancer treatments.

**Aim**
To compare response of 17-OH progesterone (17-OHP) to various doses of tetracosactide in healthy volunteers.

**Conclusions**
ACTH test is widely accepted as diagnostic tool in suspicion on peripheral as well as on central hypocorticism. The optimal dose of tetracosactide for determination of hypocorticism is still matter of debate. The 250 μg as a standard dose of tetracosactide has been approved for diagnosis of congenital adrenal hyperplasia (CAH) many years ago. Moreover, current limited availability of tetracosactide and its increased financial cost on the market raised the question whether the lower dose of tetracosactide for diagnosis of CAH may be sufficient stimulation.

**Methods**

In ten healthy volunteers (four males, median 42 years) with normal adrenal function (based on clinical and biochemical evaluation) the ACTH tests with i.v. administration of 250 μg (HDST), 10 μg (MDST), and 1 μg (LDST) tetracosactide were performed.

**Results**
Similar response in 17-OHP levels in all three variants of the test was observed. Median 17-OHP levels 30 min after the tetracosactide administration were 6.62, 6.62, and 5.68 nmol/l for HDST, MDST, and LDST respectively. 60 min after the administration the median levels were 6.93, 5.91, and 4.70 nmol/l.

**Conclusion**
Our data support the hypothesis of ACTH test reliability for the diagnosis of CAH in all variants with lower doses of ACTH compared to standard dose. Further confirmation of our observation in patients with known non-classical form of CAH would be appropriate.

**Disclosure**
This work was supported by grant number NT 11277-6 of the IGA MZCR.

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Introduction
Adrenocortical oncocytomas are rare seen tumours. Most of these tumours are benign and non-functioning. We present here a case of oncocytic adrenocortical tumour, detected incidentally, presented with Cushing’s syndrome.

Case
A 41-year-old male patient, while investigating for abdominal pain, bilateral adrenal masses were detected in abdominal ultrasonography and was admitted to Endocrinology Clinic. He had no history of hypertension. Physical examination revealed, a pulse rate of 80 beats/min and a blood pressure of 180/90 mmHg.

Patient had typical cushingoid appearance including a plethora moon face, truncal and centripetal obesity and abdominal cutaneous striae. In his laboratory investigations; glucose level was 97 mg/dl, ALT 80 U/l (30–65), cortisol 18.47 µg/dl (5–23), DHEAS > 1000 µg/dl (35–560), and ACTH < 5 pg/ml (9–52). In the 24 h urine metanephrine level, normetanephrin and plasma aldosteron concentration, plasma renin concentration were normal. Other biochemical blood test results were within normal ranges. The plasma cortisol level was 24 µg/dl after 1 mg overnight, 22 µg/dl after 2 days 2 mg dexamethasone suppression test, and midnight cortisol was 14 µg/dl. According to these findings Cushing’s syndrome was considered. Surrenal magnetic resonance imaging (MRI) that showed bilateral adrenal adenomas that were 35 × 32 mm in size in the right and 78 × 64 mm in the left adrenal gland, isointense in T1A and T2 and included cystic regions. Left adrenalectomy was performed to the patient. The postoperative histopathological diagnosis was borderline oncocytic adrenocortical tumour with myelolipoma foci and Ki-67 proliferation index was under 1%. The patient is still under follow-up at our clinic with the replacement therapy of steroid.

Conclusion
The incidence of adrenal incidentaloma is increasing according to technological development and frequency of radiological imaging. Adrenocortical oncocytomas are rare seen tumours. Most of these tumours are benign and non-functioning. Some of that tumours are malign and while the others are borderline. Oncocytic neoplasms microscopically consist of so called oncocytes, large cells with rich eosinophilic granulations due to high concentration of mitochondria. We present a case with oncocytic adrenocortical tumour presented with Cushing’s syndrome because it is seen rare.

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EP53
Beneficial effects of replacement therapy with modified-release hydrocortisone in patients with adrenal insufficiency
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Introduction
The classical replacement therapy for hypoadrenalism may expose patients to non-physiologic glucocorticoids levels with negative metabolic consequences. The classical replacement therapy for hypoadrenalism may expose patients to non-physiologic glucocorticoids levels with negative metabolic consequences. Up to now, one study demonstrated that, as compared to the classical treatment, a modified-release hydrocortisone (MRH), improves weight, blood pressure, glycaemic control and QoL in a 3-month follow-up period. Few data are available on the long-term persistence of these benefits.

Design/methods
Ten patients with Addison’s disease and seven with central hypocortisolism (mean ± s.d., age 50.8 ± 10.7 years, BMI 27.9 ± 7.0 kg/m², 9M/8F) were enrolled in three Italian Endocrine Units. 12 patients were treated with cortisone acetate (30.2 ± 10.9 mg/day), five patients with hydrocortisone (25 ± 5 mg/day), with an inadequate control of the disease. 80% of patients reported fatigue. In all patients, after baseline evaluations, the classical therapy was replaced with MRH (20.3 ± 1.2 mg/day). At 1, 3, 6, and 12 months after the therapy modification (mean follow-up: 8.8 ± 4.2 months) we evaluated parameters of adrenal function, BMI, blood pressure, HbA1c levels, and symptoms of over- or under-treatment.

Results
MRH caused higher morning cortisol levels than the classical therapy (after 12 months: 20.7 ± 6.5 µg/dl vs 13.2 ± 3.5 µg/dl, P = 0.02), but comparable UFC values (after 12 months: 29.1 ± 14 µg/24 h vs 24.1 ± 9.5 µg/24 h, P = 0.299), confirmed at each evaluation. In Addisonian patients MRH did not influence ACTH levels over time (after 12 months: 175.8 ± 215 µg/ml vs 150 ± 6.175 µg/ml, P = 0.781). Paired sample T-test showed that metabolic parameters did not change after 1, 3, and 6 months. The ten patients that completed the 12 months follow-up, showed a reduction of BMI (29.2 ± 5.8 vs 28.3 ± 5.2, P = 0.027) and systolic (126 ± 18 mmHg vs 115 ± 18 mmHg, P = 0.03) blood pressure, while HbA1c decreased in the two diabetic patients (8.1 ± 0.7% vs 5.9 ± 1.1%), 60% of patients showed an improvement of fatigue after 6 months (P = 0.023) that persisted at 12 months.

Conclusion
In patients with hypoadrenalism, a 12 months treatment with MRH seems to improve some metabolic parameter and to reduce weakness.

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EP54
A phase 1, randomised, open-label, four-period crossover, single-dose study to evaluate the pharmacokinetics of hydrocortisone modified release tablets
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Novel biopharmaceutical techniques have allowed the development of a hydrocortisone modified release (MR) tablet (once-daily administration for replacement therapy in adrenal insufficiency) mimicking more closely the physiological serum cortisol profile. Robust bioavailability is needed to secure this new treatment safety.

Aims
To compare single-dose pharmacokinetics (PK) of MR tablets manufactured at two different sites by assessing intra-subject variability (dose range: 5–20 mg).

Methods
Thirty-two healthy men and women (20–55 years; BMI: 18–30 kg/m²) were enrolled into a randomized, open-label, four-period crossover, single-dose PK study with collection of baseline 24 h endogenous cortisol secretion. During four periods 5, 15, 20 mg (new manufacturing site R), and 20 mg (reference site G) were administered orally at 0800 h after overnight fast. Endogenous cortisol secretion during PK sampling was suppressed using dexamethasone. PK parameters were determined using non-compartmental analysis. Plasma cortisol was measured using LC–MS/MS.

Results
Within-individual comparison between the endogenous profile and the 20 mg tablet showed hydrocortisone treatment provided higher than endogenous concentrations 0–4 h post-dose and similar concentrations 5–15 h post-dose. Mean hydrocortisone Cmax (s.d.) was 82.0 (18.2), 148.8 (29.3), 177.1 (25.5), and 178.0 (28.1) ng/ml and mean AUC(0–4 h) was 532.8 (128.0), 1024.5 (185.1), 1178.2 (222.2), and 1191.4 (190.9) ng·h/ml for 5, 15, 20 mg treatments, and 20 mg G treatment respectively. Bioequivalence, defined as the 90% CI being within the 80–125% limits, was demonstrated. Within-subject variability was below 15% for all examined PK parameters for the 20 mg R and G MR tablet oral administration. Exposure PK parameters were found to be less than dose proportional, i.e. AUC(0–4) with a 78% slope (95% CI: 0.70–0.85) in the 5–20 mg dose range.

Conclusions
Once daily MR hydrocortisone demonstrates a physiological cortisol exposure during the day. Within-individual day-to-day PK variability is very low underpinning product safety for replacement therapy. Hydrocortisone PK is less than dose proportional, an important PK property of oral hydrocortisone that should be considered in the intercurrent illness management of adrenal insufficiency.

Disclosure
This work was supported by Shire.

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EP55
Rare case of ectopic ACTH secreting tumour causing cyclical Cushing’s syndrome
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We are reporting a rare case of ectopic ACTH secreting tumour causing cyclical Cushing’s syndrome. A 63-year-old lady presented in March 2013 with tiredness and bilateral leg swelling and weakness associated with easy bruising. She was admitted to local hospital in April 2013 with worsening proximal myopathy and
Review of clinical presentation of primary hyperaldosteronism and identify unique features in our cohort

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Aim
Review of clinical presentation of primary hyperaldosteronism (PHA) and identify unique features in our cohort.

Method
Patients with PHA were identified from patients who underwent adrenal vein sampling (AVS) at our centre until October 2014.

Results
45 PHA patients (32 males, mean age of 50 years, 33 older than 45 years) were identified after confirmation with high aldosterone:renin ratio >15 and/or positive saline suppression test. All had hypertension and 41/45 (91.1%) presented with hypokalaemia. CT adrenal findings were; 31/45 (68.9%) unilateral nodule (one had two nodules unilaterally), 5/45 (11.1%) bilateral nodules, 7/45 no nodules, 1/45 bilateral bulky adrenals, and 1/45 left adrenal limb thickening. The mean tumour size on CT was 1.41 (0.7–2.3) cm. All underwent AVS (four had repeat investigation). Based on biochemical criteria, 61% (28/45) of cases were successfully cannulated bilaterally. Final diagnosis of PHA was established after evaluating both CT and AVS findings (ratio of higher over lower aldosterone/cortisol of > 4 for aldosterone producing adenoma (APA) and < 3 for bilateral adrenal hyperplasia (BAH)) by the primary clinician: 18 had APA, 16 had BAH, and 11 were inconclusive. 17/45 (37.8%) patients underwent surgery (all confirmed as APA on histology). After surgery, hypokalaemia normalised in all, 15/17 (88.2%) BP improved and 3/17 (17.6%) were cured of hypertension. Among 27 patients treated medically, 25/27 (92.6%) had normalisation of potassium, 25/27 (92.6%) BP improved and 2/27 (7.4%) were cured of hypertension. One patient declined treatment.

Discussion
The prevalence of BAH is higher in our cohort compared to reported series but this could be due to selection of cases through AVS procedure as some cases of APA may have been missed because they did not undergo AVS. The prevalence of inconclusive diagnosis after AVS was higher, which could be related to the expertise in our centre.

EP56

Diagnosis of Cushing’s syndrome using scalp hair cortisol

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Background
Endogenous Cushing’s syndrome (CS) is caused by overproduction of cortisol. Current first-line screening tests for CS can produce false positive results due to medication use and stress, rely heavily on patient adherence to sampling instructions, and only measure short-term cortisol exposure which limits sensitivity. In general multiple tests are required to establish a diagnosis. Hair cortisol concentrations (HCC) offer a minimally invasive way to measure long-term cortisol exposure over months of time, and are a promising additional screening tool for CS. In addition, HCC can be used to create retrospective timelines of cortisol exposure.

Methods
We collected scalp hair from patients suspected of CS in a single academic medical center, and in healthy controls. HCC were measured using ELISA. Receiver operator curve (ROC) analysis was used to determine the optimal cut-off for CS.

Results
HCC levels were available in 35 patients with CS, 20 patients in whom the diagnosis CS could be rejected during diagnostic work-up (non-CS patients), and 174 healthy controls. HCC were higher in CS patients than in non-CS patients and healthy controls (157.6 vs 9.7 and 8.4 pg/mg, respectively, P < 0.001). At a cut-off of 31.1 pg/mg, HCC could differentiate between CS patients and healthy controls with a sensitivity of 94% and a specificity of 90%. With non-CS patients as a reference, sensitivity and specificity remained similar (94 and 90% respectively).
Prevalence of CS without specific signs is thought to be high, which might be an indication for its general screening. However, conclusive data about its diagnostics is absent. Design 189 overweight patients were studied. Nobody had clinical evidence of hypercortisolism. Diagnostic of CS was 1-mg overnight dexamethasone suppression test (1-mg DST; cut off 50 nmol/l) as a screening; midnight plasma cortisol (MPC) (< 207 nmol/l) and 24-h urinary free cortisol (UFC) (< 180 µg/24 h) as a confirmatory tests; morning plasma ACTH (5–46 pmol/l), 8-mg DST and imaging studies as topical diagnostics. Results Among 189 patients 166 were excluded to have CS according to results of DST 1 mg (< 50 nmol/l), 23 had impaired result of 1-mg DST. Among these 23 patients there were diagnosed four cases of corticotropicomas, two cortico-steromas. Other 17 patients were excluded to have CS by long-term follow-up and, therefore, they had falsely positive results of confirmatory tests. The diagnostic characteristic of MPC and UFC with established cut off were calculated: MPC - Sen 83.33% (95% CI 35.88–99.58), Sp 63.64% (95% CI 30.79–89.07), LR+ 2.29, LR− 0.26, DOR 8.75 (95% CI 0.73–103.82), UFC – 83.33% (95% CI 35.88–99.58), Sp 18.18% (95% CI 2.26–51.78), LR+ 1.02, LR− 0.92, DOR 1.11 (95% CI 0.07–15.53). In order to adjust diagnostic efficiency without a certain threshold value, the logit regression equation was calculated. The percent of concordance for UFC made 53%, MPC – 81.8%. Also there were performed comparison results of patients with and without CS: results of MPC (significant difference) and UFC (insignificant difference). Conclusions High prevalence of CS without specific signs was confirmed on our study (about 3%). Among tests used to screen and confirm CS without specific signs, UFC has the worst diagnostic characteristics and, therefore, should not be used. MPC has better characteristics, however, the question of threshold value has to be discussed.

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**EP61**

**The utility of current guidelines in the assessment of adrenal incidentalomas**

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Adrenal incidentaloma’s are a common clinical dilemma with increasing utilisation of cross-sectional imaging modalities. The aims of management include i) exclusion of possible malignancy and ii) identification of hormonally active lesions. Our unit has adopted AACE guidelines, including a screen for adrenal androgen hypersccretion. This audit aimed to review the utility of such an approach. We identified case notes of 100 consecutive adrenal incidentalomas’s referred to endocrinology prior to November 2014. All were subject to radiological scrutiny by a dedicated radiologist, whilst endocrine investigations, including two 24 h urinary metanephrines, 1 mg overnight dexamethasone suppression test, renin:aldosterone ratio and DHEAS were arranged, together with electrolytes and blood pressure. Radiologically, 84% were considered to be benign adrenal adenomas on the basis of either CT density (< 10 HU), CT contrast washout at 10 min (>60%) or in and out of phase MRI. 3% were myelolipomas and 4% phaeochromocytomas. 8% were indeterminate and referred for further investigation or surgery. From a functional perspective, we identified four phaeochromocytomas, all of whom had imaging studies inconsistent with a benign adenoma and raised urinary metanephrines. Five had a 0900 h cortisol of > 100 following 1 mg dexamethasone, none of whom had symptoms/signs consistent with cortisol excess and two of whom had already had cortisol excess excluded by further investigation. The remainder have further investigations pending. Two males had elevated DHEAS levels and both had abnormal imaging, one of which proved to be a phaeochromocytoma. There were no abnormal renin:aldosterone ratios. 89% of the cohort was hormonally inactive. On the basis of this audit, we are concerned that adrenal incidentalomas are currently over-investigated. In patients with no symptoms/signs of an underlying endocrinopathy, normal blood pressure, normokalaemia and imaging consistent with a benign adenoma, universal endocrine investigation is largely unrewarding.

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**EP59**

**Role for 131I-6β-iodomethyl-norcholesterol scintigraphy in subclinical Cushing’s syndrome with bilateral adrenal lesions**

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Introduction Subclinical Cushing’s syndrome (SCS) is the most frequent endocrine dysfunction found in adrenal incidentalomas. Although adrenalectomy constitutes a therapeutic option for selected cases, the presence of bilateral tumours can difficult the surgical decision. Objective Evaluate the utility of 131I-6β-iodomethyl-19-norcholesterol scintigraphy in SCS with bilateral adrenal tumours. Methods Retrospective analysis of all patients with SCS and bilateral adrenal lesions submitted to 131I-6β-iodomethyl-norcholesterol scintigraphy in our Nuclear Medicine Department. Following suppression with dexamethasone, planar thoracoabdominal scintigraphy, and single photon emission computed tomography (SPECT/CT) images were obtained at 3rd, 5th, and 7th days after i.v. administration of 1 mCi of 131I-6β-iodomethyl-19-norcholesterol. Results Five scintigraphy were performed in four women, aged 57.5 years (46–67 years), with SCS and bilateral incidentalomas identified by abdominal CT: at right with a median diameter of 19 mm (17–35 mm) and at left with 18 mm (7–28 mm). All patients presented osteoporosis; two had dyslipidaemia and two had arterial hypertension. Two patients showed radiopharmaceutical uptake at right adrenal with non-visualisation of contralateral gland: both were proposed to adrenalectomy. Histopathological study confirmed the adrenal cortical adenoma. After surgery, a significant improvement of their comorbidities was observed with reduction of anti-hypertensive drugs. Other patient exhibited symmetrical uptake and was maintained on medical treatment. In the fourth patient, both the first scintigraphy and adrenal vein sampling were inconclusive. However, after a second scintigraphy that suggested a hyperfunctioning right adenoma, she was submitted adrenalectomy that confirmed the lesion. Conclusions This work suggests a high resolution of the adrenal 131I-6β-iodomethyl-19-norcholesterol scintigraphy, providing a more precise picture of functional structural lesions that crosses the information obtained by CT and hormonal assays. In these patients ended a more targeted surgical approach, preserving the other adrenal and improving their comorbidities.

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**EP60**

**Diagnostic pitfalls of Cushing’s syndrome without specific clinical signs among patients with obesity**

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Introduction

Prevalence of CS without specific signs is thought to be high, which might be an indication for its general screening. However, conclusive data about its diagnostics is absent. Design 189 overweight patients were studied. Nobody had clinical evidence of hypercortisolism. Diagnostic of CS was 1-mg overnight dexamethasone suppression test (1-mg DST; cut off 50 nmol/l) as a screening; midnight plasma cortisol (MPC) (< 207 nmol/l) and 24-h urinary free cortisol (UFC) (< 180 µg/24 h) as a confirmatory tests; morning plasma ACTH (5–46 pmol/l), 8-mg DST and imaging studies as topical diagnostics. Results Among 189 patients 166 were excluded to have CS according to results of DST 1 mg (< 50 nmol/l), 23 had impaired result of 1-mg DST. Among these 23 patients there were diagnosed four cases of corticotropicomas, two cortico-steromas. Other 17 patients were excluded to have CS by long-term follow-up and, therefore, they had falsely positive results of confirmatory tests. The diagnostic characteristic of MPC and UFC with established cut off were calculated: MPC – Sen 83.33% (95% CI 35.88–99.58), Sp 63.64% (95% CI 30.79–89.07), LR+ 2.29, LR− 0.26, DOR 8.75 (95% CI 0.73–103.82), UFC – 83.33% (95% CI 35.88–99.58), Sp 18.18% (95% CI 2.26–51.78), LR+ 1.02, LR− 0.92, DOR 1.11 (95% CI 0.07–15.53). In order to adjust diagnostic efficiency without a certain threshold value, the logit regression equation was calculated. The percent of concordance for UFC made 53%, MPC – 81.8%. Also there were performed comparison results of patients with and without CS: results of MPC (significant difference) and UFC (insignificant difference). Conclusions High prevalence of CS without specific signs was confirmed on our study (about 3%). Among tests used to screen and confirm CS without specific signs, UFC has the worst diagnostic characteristics and, therefore, should not be used. MPC has better characteristics, however, the question of threshold value has to be discussed.

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EP62
Prospective evaluation of cardiovascular risk in subclinical Cushing’s syndrome
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Introduction
Natural history of adrenal incidentalomas has not been totally understood. Current data from subjects with adrenal incidentalomas demonstrated an increased rate of metabolic disturbances and cardiovascular risk. It has been shown that subjects with subclinical cortisol excess were more susceptible to diabetes, hypertension, and obesity. However, there is no data regarding prospective cardiovascular risk evaluation in subjects with subclinical Cushing’s syndrome.

Methods
Patients referred to Dokuz Eylul University between January 2013 and January 2014 were included. Patients with subclinical Cushing’s syndrome (n=20), patients with non-functioning adrenal adenomas (n=30) and subjects without adrenal adenomas (n=25) were enrolled. Interventions included physical examination, anthropometric measures, imaging with CT (MRI if CT was contraindicated), 1 mg DST, ACTH, UFC, urinary catecholamine levels, PAC/PRA (if indicated), hsCRP, lipid profile, HOMA index, and fibrinogen levels. Additionally all subjects underwent carotid intima media thickness (IMT) measurement and evaluation of flow mediated dilatation (FMD) of the brachial artery. All laboratory tests were repeated in both groups after 12 months follow up.

Results
Baseline anthropometric parameters were comparable. Briefly, patients with subclinical Cushing’s syndrome did not exhibit any deteriorations in IMT of the carotid arteries or FMD of brachial artery after 12 months follow up.

Discussion
Although subclinical Cushing’s syndrome is associated with several cardio-metabolic disturbances, endothelial function does not seem to be altered in 12 months follow up. Therefore, the decision of adrenalectomy vs follow up should be conservative and short-term follow up seems feasible.

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EP63
Salivary cortisol values among nurses at Pathology and Emergency Department
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Aim
To see the difference between salivary cortisol values and correlation with the work stress.

Methods
The salivary and serum cortisol values were analysed in two groups of nurses, six nurses in the Emergency Department and six nurses in the Pathology Department at our hospital, three females and three males for each group. The samples were taken before beginning the work and after finishing the work. The cases respected all the rules for salivary testing of cortisol and the average age of the participants was the same for both groups, 28.5 years old.

Results
Median salivary cortisol values in the Emergency Department in the morning were 188.8 nmol/l (normal range 55–230) and median salivary cortisol values 3.1 μg/dl (normal range 1–11.3) and at the end of work (1600 h) the values were: serum cortisol values 130.2 nmol/l (normal range 28–140) and salivary cortisol values 1.87 μg/dl (normal range 0.2–2.7). In the Pathology Department: in the morning (0800 h) average serum cortisol values were 125 nmol/l and salivary cortisol values 2.1 μg/dl and at the end of the work (1600 h): serum cortisol values were 94.0 μmol/l and salivary cortisol values 1.22 μg/dl.

Conclusions
Since the stress of work is higher in the Emergency Department, even the results of the salivary cortisol values were higher in the nurses of the Emergency Department compared to the nurse of Pathology Department and there existed a correlation between salivary and serum values, but the study needed a bigger group of nurses to have more trustful conclusions.

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EP64
Serum brain-derived neurotrophic factor in Cushing’s syndrome patients
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Introduction
Brain-derived neurotrophic factor (BDNF) is a protein that has been linked to several cardiovascular risk factors and bone status. Stress and corticosteroid exposure can affect BDNF levels, although this has never been studied in Cushing’s syndrome (CS). The aims of this study were to establish if BDNF levels were reduced in CS and to check possible associations to cardiovascular risk factors and bone status.

Methods
52 patients (18 active CS and 34 in remission) and 52 controls matched for sex and age were studied. Blood tests (including biochemistry, cortisol, and BDNF), anthropometry, complete clinical examination and a whole body DEXA were performed. Statistical analysis was performed using ANOVA with Bonferroni correction and Pearson correlations.

Results
BDNF was reduced in both active and in remission CS patients, compared to controls (P<0.001 and P<0.05). Both patient groups had higher waist (P<0.01 and P<0.05) and diastolic blood pressure (P<0.001 both), while CS in remission also showed higher systolic blood pressure (P<0.01) and triglycerides (P<0.01) than controls. Correlations including the whole sample showed that BDNF positively correlated with bone mineral content (r=0.285, P<0.01), meaning that reduced BDNF indicated less bone mineral content. BDNF also negatively correlated to diastolic blood pressure (r=-0.210, P<0.05).

Conclusion
BDNF is reduced in CS patients, even after cure. It may contribute to persistent comorbidities seen in CS patients, such as osteoporosis and hypertension.

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Disclosure
This work was supported by the Instituto de Salud Carlos III (grant number FIS 080302) and the Public Health Program of the European Comission (ERCUSYN project, grant number PHP 800200).

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EP65
Urinary metanephrine levels can be spurious in the diagnosis of patients with phaeochromocytoma: preliminary results from a single centre
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Introduction
Phaeochromocytomas (PHEO) are diagnosed with classic findings and symptoms but biochemical confirmation must be made. Either urinary or plasma catecholamines and metanephrines can be used for biochemical evaluation. Normal values rule out the diagnosis, whereas fourfold increase above the upper limit of normal confirm the diagnosis. But value of borderline levels can be spurious in the diagnosis of patients with subclinical cortisol excess. The aim is to determine the urinary fractionated metanephrine and catecholamine levels in patients with PHEO.

Material and methods
Thirteen patients with final diagnosis of PHEO (PHEO group) and ten patients (non-PHEO group) who underwent adrenalectomy and finally diagnosed as benign neoplasm (six adenomas, three cysts, and one hyperplasia) were evaluated retrospectively. Urinary metanephrines were evaluated by HPLC.

Disclosure
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Results

In PHEO group urinary metanephrines were as follows: 3 (25%) had borderline elevations, 9 (75%) had normal values, however 1 (10%) had borderline elevations, 1 (10%) had sixfold elevations, and 8 (60%) had normal values in non-PHEO group. The difference was evaluated as statistically insignificant (P = 0.19). Normetanephrine values were as follows: borderline elevation in 5 (41.7%), twofold elevation in 1 (8.3%), sixfold elevation in 1 (8.3%), and normal values in 5 (41.7%). Pauci and bilateral adrenal hyperplasia, the two most common subtypes of primary aldosteronism (PA). However, AVS protocols are not standardised and vary between centres. The objective of the present study was to assess whether the postoperative clinical and biochemical parameters in patients who underwent unilateral adrenalectomy for PA.

Conclusion

Overall, 82% of patients displayed CL suppression at AVS, with no statistically significant differences among centres. This percentage was significantly higher in non-PHEO group (P = 0.02). This inhibitory effect was also confirmed by [3H]thymidine incorporation assay. Moreover, combining metformin and mitotane leads to a synergistic effect which reduces cell viability more than metformin alone (IC50 0.3 mM). To further investigate the molecular mechanisms by which metformin inhibits cell growth, we performed western blot analysis after 6 h treatment with different doses of metformin (20, 50, and 100 mM), and 24 h treatment with different doses of metformin (0.5–250 mM). Adrenocortical carcinoma (ACC) is a rare, heterogeneous malignancy with a poor prognosis, particularly when metastatic at diagnosis. To date, radical surgery, possibly associated with mitotane adjuvant therapy, is the only available treatment. However, the mean 5-year survival rate drops under 10% in metastatic ACC and chemo-resistance often develops. Thus, more specific and effective drugs for ACC treatment are urgently required. The antiadibolic drug metformin, used in type 2 diabetes treatment, has been associated with decreased cancer incidence and mortality in several human cancers, suggesting us the possibility to test its potential efficacy on ACC too.

Conclusions

For patients with late onset (LO) phenotype (manifested commonly during puberty), 5 (41.7%) had elevated metanephrines compared with basal procedures (90% vs 77%). The CL ratio was inversely correlated with the aldosterone level at diagnosis and, among AVS parameters, with the lateralisation index (P < 0.02 and P < 0.01 respectively). To investigate whether the presence of CL suppression was correlated with response to adrenalectomy, we analysed the CL suppression status with regard to the patient’s clinical and biochemical postoperative parameters. No differences were observed between the two groups for the main clinical and biochemical parameters (systolic and diastolic blood pressures, aldosterone, PRA, PRC, K+, number of drugs, reduction of blood pressure levels, and the number of classes of drugs assumed), but patients with CL suppression underwent a significantly larger reduction in aldosterone levels after adrenalectomy.

Conflict of interest

The authors declare no competing personal or financial interests.

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EP66

Clinical significance of contralateral adrenal suppression during adrenal vein sampling in primary aldosteronism

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Objective

Adrenal vein sampling (AVS) is recognised by Endocrine Society guidelines as the only reliable mean to distinguish between aldosterone producing adrenomas and bilateral adrenal hyperplasia, the two most common subtypes of primary aldosteronism (PA). However, AVS protocols are not standardised and vary between centres. The objective of the present study was to assess whether the presence or absence of contralateral adrenal (CL) suppression has an impact on the postoperative clinical and biochemical parameters in patients who underwent unilateral adrenalectomy for PA.

Design and methods

The study was retrospectively carried out in eight referral hypertension centres in Italy, Germany, and Japan. Screening and subtype differentiation were performed according to the Japan Endocrine Society and the Endocrine Society guidelines and a total of 234 AVS procedures were included in the study. CL suppression was defined as aldosterone/cortisol ratio after adrenalectomy of aldosterone/cortisol before adrenalectomy <1.

Results

Overall, 82% of patients displayed CL suppression at AVS, with no statistically significant differences among centres. This percentage was significantly higher in non-PHEO group (90% vs 77%). The CL ratio was inversely correlated with the aldosterone level at diagnosis and, among AVS parameters, with the lateralisation index (P < 0.02 and P < 0.01 respectively). To investigate whether the presence of CL suppression was correlated with response to adrenalectomy, we analysed the CL suppression status with regard to the patient’s clinical and biochemical postoperative parameters. No differences were observed between the two groups for the main clinical and biochemical parameters (systolic and diastolic blood pressures, aldosterone, PRA, PRC, K+, number of drugs, reduction of blood pressure levels, and the number of classes of drugs assumed), but patients with CL suppression underwent a significantly larger reduction in aldosterone levels after adrenalectomy.

Conclusions

For patients with late onset (LO) phenotype (manifested commonly during puberty), 5 (41.7%) had elevated metanephrines compared with basal procedures (90% vs 77%). The CL ratio was inversely correlated with the aldosterone level at diagnosis and, among AVS parameters, with the lateralisation index (P < 0.02 and P < 0.01 respectively). To investigate whether the presence of CL suppression was correlated with response to adrenalectomy, we analysed the CL suppression status with regard to the patient’s clinical and biochemical postoperative parameters. No differences were observed between the two groups for the main clinical and biochemical parameters (systolic and diastolic blood pressures, aldosterone, PRA, PRC, K+, number of drugs, reduction of blood pressure levels, and the number of classes of drugs assumed), but patients with CL suppression underwent a significantly larger reduction in aldosterone levels after adrenalectomy.

Conclusion

The GLC receptor polymorphisms are not associated with the therapy efficacy in adult, Hungarian patients with 21-hydroxylase deficiency.

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Background

Congenital adrenal hyperplasia (CAH) is an autosomal recessive inherited disorder caused by 21-hydroxylase deficiency in 95% of all cases. Two main clinical subtypes: the classical (manifested after birth, or in early newborn period) and the late onset (LO) phenotype (manifested commonly during puberty). The lifelong glucocorticoid (GC) supplementation is essential in therapy of these patients. Response to GC therapy is individual and partly genetically determined.

Objective

Our aim was to study the effect of three well-known polymorphisms (SNPs; BclL, N363S, A3669G) of the GLC receptor on clinical, laboratory, and GC supplementation dosage in adult Hungarian patients with 21-hydroxylase deficiency.

Patients and methods

The diagnosis of 21-hydroxylase deficiency was based on clinical, laboratory, and molecular genetic tests including the identification of the most common CYP21A2 gene mutations and determination of the allelic copy number (CN) of the CYP21A2 gene. In 93 patients (54 classical and 39 late-onset, age: 28.8 ± 13.7 years), with 21-hydroxylase deficiency the BclL and N363S polymorphisms were measured using allele-specific PCR, the A3669G polymorphism and the CN variations were detected by real-time qPCR. Allele frequencies of GR polymorphisms were compared to a Hungarian, control population (n = 160). Association between GR SNPs and clinical, hormone laboratory, and GC supplementation dosage was studied.

Results

No significant differences among centres. The CN of the CYP21A2 gene was also statistically insignificant (P = 0.03). There were also no significant differences in urinary adrenaline and noradrenaline levels between groups.

Conclusion

GLC receptor polymorphisms are not associated with the therapy efficacy in adult, Hungarian patients with 21-hydroxylase deficiency.
EP69
Prevalence and natural history of adrenal incidentalomas: a prospective cohort study
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Introduction
Adrenal incidentalomas (AIs) are frequently detected due to the increasing use of abdominal imaging for diagnostic purposes. However, few prospective studies exist with respect to their natural history, regarding their size and clinical course. The aim of this study was to report the prevalence and natural history of AIs.

Methods/design
Interim analysis of a prospective cohort study. The following tests were performed: serum cortisol nocturnal rhythm, 24 h-urinary free cortisol, low-dose dexamethasone suppression test, aldosterone to plasma-renin-activity ratio and 24 h-urinary total metanephrines and catecholamines. In cases of positive results, confirmatory tests were performed. Radiological assessment was repeated at 6–12 months and yearly thereafter.

Results
Sixty-four patients (19 (30%) males, mean age 59.7 ± 12.1 years) were included. Follow-up data were available for 57 AIs (median time: 36 months, range 4–84). Median size was 2.5 mm (range 0.5–6.5) (unilateral adenoma in 78%). The final diagnosis was: 56 non-functioning adenomas (87.5%), 5 (7.8%) subclinical Cushing’s syndrome (SCS), 1 (1.6%) phaeochromocytoma, 1 (1.6%) aldosteronoma, and two adrenocortical carcinomas (3.2%), of which one had also SCS. Mass enlargement (9 mm) was observed in one patient (2.8%), while a decrease (7–27 mm) in 3 (8.5%). No hormonal evolution was noticed. Regarding glucose metabolism, 12, 16.7, and 20% of the patients presented deterioration in glucose metabolism at the first, second, and third year of follow-up respectively. The respective percentages for dyslipidaemia were 26, 43, and 44% and for hypertension or blood pressure worsening were 38, 44, and 48%. After excluding those with SCS, these percentages did not alter significantly. New cardiovascular events or fractures were recorded in 7.8% of the patients.

Conclusions
The vast majority of AIs involved benign, non-secretory masses. Mass enlargement was rare. More than one-third of patients developed hypertension or their lipid profile worsened, while one fifth showed deterioration in glucose metabolism, irrespectively of the presence of SCS.

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EP70
Prevalence of hypercortisolism in type 2 diabetes patients: a meta-analysis
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Background
Type 2 diabetes (T2D) and hypercortisolism associated with Cushing’s syndrome (CS) share clinical characteristics such as hypertension, dyslipidaemia, hyperglycaemia, and obesity. Several studies have recorded a relatively high prevalence of hypercortisolism in T2D, which may have therapeutic implications. The aim of this systematic review and meta-analysis was to assess the prevalence of hypercortisolism in T2D patients.

Methods
Original articles assessing the prevalence of endogenous CS in T2D were eligible. A search was performed in SCOPUS, MEDLINE, and EMBASE. Data were pooled in a random effects logistic model.

Results
Fourteen articles were included, with a total of 2827 T2D patients. The reported prevalence of hypercortisolism in T2D ranged between 0 and 12.1%. The pooled prevalence of hypercortisolism in T2D was 3.6% (95% CI 3.0–4.4). The prevalence did not differ between studies of unselected patients and patients selected on the basis of complications such as obesity or poor glycaemic control (P = 0.41). Imaging in patients with hypercortisolism (n = 102) revealed adrenal tumour(s) and pituitary tumours in 14 and 52% respectively.

Conclusion
Hypercortisolism is a reproducible and relatively frequent finding in T2D. This observation merits continued interest.

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EP71
Fludrocortisone therapy in patients with primary adrenal insufficiency: relationships with different hydrocortisone doses
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Introduction
During recent years many authors have advocated lower hydrocortisone doses in patients with primary adrenal insufficiency (PAI) mainly due to worries for non-physiological effects like increased cardiovascular risk and bone resorption, but very little attention has been drawn to fludrocortisone dosing. Our main hypothesis was that that the higher hydrocortisone dose, the lower the fludrocortisone dose and vice versa.

Design
The European Adrenal Insufficiency Registry (EU-AIR) sponsored by Shire with 20 centers in Germany, The Netherlands, Sweden and the UK started enrolling patients with AI in August 2012. At enrolment, comprehensive demographic and baseline data, etiology of PAI, details of glucocorticoid replacement therapy and safety data (intercurrent illnesses, adrenal crisis) are collected electronically. This report compares baseline data of PAI (including classic adrenal hyperplasia (CAH)) treated with hydrocortisone/cortisone acetate or the new modified fludrocortisone dose and visit versa.

Results
As of 5th November 2014, 345 patients with PAI, 50.1 ± 15.7 years, 221 (64.1%) F, BMI < 25 44.1%, 25 < 30 30.4% and ≥ 30 18% (missing BMI data 7.5%), were registered in EU-AIR. The distribution of hydrocortisone-equivalent doses were: n = 179 received ≤20 mg, while n = 166 received >20 mg (of those n = 27 received > 30 mg). The median fludrocortisone dose for all patients was 100 μg (range 0–300). No clear differences were found between gender, but a tendency to higher doses of fludrocortisone in males, if treated with hydrocortisone < 20 μg, was found. On the other hand, increasing doses with fludrocortisone were slightly associated with higher BMI and with hydrocortisone doses > 30 mg.

Conclusions
Our data shows that the fludrocortisone dose differs widely between patients. We could not demonstrate a general effect that higher hydrocortisone doses compensating the mineralocorticoid effect with correspondingly lower doses of fludrocortisone in PAI.

Disclosure
This work was sponsored by Shire.

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EP72
Prevalence of Cushing’s syndrome at overweight and obese patients
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Background
In the presence of specific symptoms and signs, Cushing’s syndrome (CS) may be easily recognised. On the other hand, in overweight and obese patients without typical features of CS, diagnosis may be omitted. Our aim was to evaluate the prevalence of CS among overweight and obese patients.

Methods
We enrolled 264 overweight and obese patients who have not overt CS clinical features between January 2012 and December 2014 at Ankara Numune Education and Training Hospital. All patients were screened via overnight 1 mg dexamethasone suppression test (DST). Patients who had positive screening test has undergone other diagnostic tests.

Results
In eleven patients cortisol levels has not been suppressed under 1.8 μg/dl after overnight 1 mg DST. Overnight 2 mg DST cortisol levels were supressed under 1.8 μg/dl in these four patients. The remaining seven patients (five women, two men) CS were confirmed with a standard 2-day, 2-mg DST, and high late-night salivary cortisol levels (2.6%). While six of them were ACTH-dependent CS, only one were adrenal CS. Mean BMI of CS patients was 38.3 kg/m², the remainings mean BMI was 38.8 kg/m². There was four prediabetes and two diabetes mellitus patients in CS group. Four of CS patients were hypertensive.

Conclusion
We found prevalence of CS 2.6% in overweight and obese patients whether or not accompanying overt DM or HT. Overnight 2 mg DST results yielded more specific results than 1 mg DST. Based on these results we consider screening CS with 2 mg DST in this population may be reasonable.

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EP73
The clinical course of patients with adrenal incidentaloma: is it time to reconsider the current recommendations?
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Context
The current guidelines for the management of adrenal incidentaloma advise hormonal and radiological follow-up of the patients for 2–5 years after the initial diagnosis. However, a vast majority of adrenal incidentaloma are non-functional, benign cortical adenomas that require no treatment, so the routine application of the current strategies often results in a number of unnecessary biochemical and radiological investigations.

Objective
The aim of this study was to analyse the clinical course of patients with adrenal incidentaloma and to provide a critical review of the current management strategy of the disease. Design and setting: This was a retrospective study performed in the Croatian Referral Center for adrenal gland disorders. Patients: The study included 319 consecutive patients with adrenal incidentaloma 174 of which were followed for at least 24 months.

Results
A vast majority of patients were diagnosed with benign adrenal masses whereas in about 5% of them adrenal tumour corresponded to adrenal carcinoma or metastasis. Tumour density was found to be superior to tumour size in distinguishing benign adrenal masses from malignant tumors and pheochromocytomas. During the follow-up no patient demonstrated a clinically significant increase in tumour size. In addition, no changes, either in metanephrines and norepinephrine or in the activity of renin-aldosterone axis, were observed during the follow-up. Six patients developed SCS.

Conclusion
The study indicates that the risk of an adrenal mass initially diagnosed as benign and non-functional to become malignant or hormonally active is rather low. Therefore, the clinical management of those patients should be tailored on an individual basis in order to avoid unnecessary procedures.

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EP74
An audit of the investigation and follow up of adrenal incidentalomas
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An adrenal incidentaloma is defined as an adrenal mass > 1 cm diameter, discovered serendipitously on radiological imaging done for another reason. They are important because a percentage will turn out to be malignant or secrete excess hormones. The aim of the current study was to ascertain if these lesions were being investigated and followed appropriately compared to American Association of Clinical Endocrinologists guidelines. All imaging reports for the calendar year 2010 were searched for the terms ‘adrenal’ and ‘adenoma’ and then checked manually. Imaging done for staging of cancer or for investigation of possible adrenal disease was excluded. 95 patients were identified. Clinical information was obtained form the Northern Ireland Electronic Care Record and clinical notes.

The study indicates that the risk of an adrenal mass initially diagnosed as benign and non-functional to become malignant or hormonally active is rather low. Therefore, the clinical management of those patients should be tailored on an individual basis in order to avoid unnecessary procedures.

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EP75
Biochemical control and clinical improvement is induced by long-term pasireotide administration in the majority of patients with Cushing’s disease persisting after pituitary surgery
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Pasireotide (SOM230) is a multisite receptor ligand somatostatin analogue with high binding affinity to somatostatin receptor subtype 5, which is predominantly expressed in ACTH-secreting pituitary adenomas. It is indicated for the treatment of adult patients with Cushing’s disease (CD) for whom pituitary surgery is not an option or has not been curative. Our study evaluated the effects of pasireotide, administered for 12 months at a dose of 600–900 μg/daily, in 5 CD patients with persistent/recurrent disease after pituitary surgery. 24-h urinary free cortisol (UFC) levels, weight, BMI, waist circumference, blood pressure and glucose and lipid metabolism parameters were evaluated in all patients. After 6 months of therapy 4/5 patients (80%) had normal UFC levels, confirmed at 12 months. UFC normalization was associated with a slight improvement in anthropometric values and amelioration of lipid profile. In the remaining 20% of patients (1/5), normalization of UFC levels after 1 month of therapy was followed by escape from response. No patient experienced adrenal insufficiency. Hyperglycaemia due to pasireotide therapy occurred in two patients with normal glucose metabolism prior to treatment. These findings suggest that Pasireotide is an
EP76
Ectopic thyroid tissue in the adrenal gland: report of a case
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To date, intraadrenal ETT has been reported in ten cases in the literature. Only aspiration biopsy was performed and found as benign.

Background
Ectopic thyroid tissue (ETT) can be explained as the localisation of thyroid parenchyma outside the orthotopic position of the thyroid gland. It can be more easily found in the tongue, neck, mediastinum, great vessels, heart and anywhere along Wollfier area, but presentation in the adrenal glands is absolutely very rare.

Case
A 39-year-old woman was referred to our Endocrinology outpatient clinic with an incidental adrenal mass which was seen in adenomatous CT performed because of a nonspecific abdominal pain. Her abdomen CT revealed a 13 × 18 mm nonadenoma solid mass in the right adrenal gland which showed 43 Hounsfield units (HU) in precontrast series, 71 HU in portal phase and 67 HU in late phase. Endocrinologic evaluation showed that it was a non-functional tumour. Her PET scan revealed a hypermetabolic nodular lesion in the right adrenal gland and physiological FDG uptake in bilateral adnexal regions. The patient underwent surgery and histological examination showed thyroid tissue in the adrenal gland seen as large islets. No sign of atypia was observed. Immunohistochemical studies were negative for CK-19, HBME-1 and GAL-3. Patient’s thyroglobulin level was within normal ranges as 23.80 ng/ml (1.60–55). She had a subtotal thyroidectomy and a simple right adrenalectomy. Final pathological examination found as benign.

Conclusion
To date, intraadrenal ETT has been reported in ten cases in the literature. Only one of them was solid like our case, and the remaining were cystic lesions. Clinicians and pathologists must be careful during distinguishing it from metastatic thyroid cancer. For our case we planned a complementary thyroidectomy to exclude a metastatic thyroid cancer. However her PET CT scan results, thyroglobulin level, benign appearance of thyroid nodules, benign biopsy result and absence of any other solid organ metastasis may propose an existence of ETT in the adrenal gland.

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EP78
Outcomes of short synacthen test in a university teaching hospital: are baseline and time 30 min sufficient?
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Introduction
Short synacthen test (SST) has become the standard method of assessing the hypothalamic–pituitary–adrenal (HPA) axis. However, there are still variabilities in practice with regards to performing and interpreting this test in particular the need for measuring cortisol level at both time 30 and 60 min. The aim of the study was to determine the outcomes of the SST in a teaching hospital to evaluate if time 30 min is sufficient.

Methods
A retrospective review of 500 consecutive SST performed at a University teaching Hospital in Dublin between 2005 and 2012. Serum cortisol was measured at time 0, 30, and 60 min following synacthen. A cortisol level of > 500 nmol/l was considered adequate to out rule adrenal insufficiency.

Results
Of the 500 patients, 297 (59.4%) were females, and the average age was 57.4 ± 19.3 years. 215 (43%) of subjects had at least one random cortisol level checked in the preceding 6 months prior to the synacthen test date, and the mean random cortisol for those who passed the test was 367.6 ± 195.7 nmol/l compared to 133.5 ± 81.8 in those who failed it, P < 0.01. 225 (45%) of patients had at least one low serum sodium (< 135 mmol/l) during the 6 months prior to test. Hyponatraemia was more prevalent in those who failed the test compared to those with adequate cortisol response (58% vs 43%, P < 0.05). 436 (87.6%) patients passed their SST at both time 30 and 60 min and 53 (10.6%) failed it. In nine cases only (1.8%), the peak value of > 500 nmol/l was achieved at time 60 but not at time 30 min.

Conclusion
Our data shows that patients with low random cortisol and hyponatraemia in the 6 months prior to the SST are likely to fail it. Measuring the baseline and time 30 min cortisol will lead to the correct diagnosis in over 98% of cases. Checking cortisol level at time 60 is of little added value in the majority of cases.

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Endocrine Abstracts (2015) Vol 37
EP79
Functional muscle capacity and daily physical activity deficits in patients with endogenous Cushings syndrome
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Cushing’s syndrome (CS) is a disease entity that through hypercortisolism affects all body’s tissues leading to increased morbidity, decreased quality of life and mortality. Muscles are among the tissues primarily affected. However, data on the impact of endogenous hypercortisolism on functional muscle capacity and daily physical activity levels are scarce. We studied 23 subjects with endogenous CS (mean age: 40.73 ±2.17 years) and 22 healthy aged and sex matched controls. Assessment of the degree of hypercortisolism was based on cortisol day-curve, midnight cortisol and 24 h urine cortisol levels (UFC). Body composition was measured by bioelectrical impedance method (BIA). Functional capacity was assessed by the 6-min walking distance test (6MWT) and by quadriceps muscle strength and endurance during maximal isometric voluntary contraction test (QMVC). Respiratory muscles strength was assessed during maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) manoeuvres. Daily physical activity in terms of number of steps (steps/day) and body movement acceleration (Actigraph GT3X) during 7 consecutive days. The fat mass was greater in CS patients compared to controls (P=0.005). No differences were found between the two groups in the parameters of MIP (P=0.79) and MEP (P=0.66). Muscle force and endurance were significantly compromised in patients with CS (P=0.04). Six minute walking distance covered was lower in CS group (P<0.001). In addition, 6MWT was well correlated with time lapse since diagnosis (P=0.02). Daily physical activity levels were lower in CS group compared to controls (steps/day, P=0.0001, and VMU/min, P=0.0001). Finally, there was a strong negative correlation between daily physical activity in terms of body movement acceleration (VMU/min) and biochemical indices of hypercortisolism. In conclusion, endogenous hypercortisolism has a profound negative influence on various parameters related to functional capacity and daily physical activity and these measurements may be a useful tool.

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EP80
Metabolic abnormalities in patients with nonfunctional adrenal incidentaloma: random or causal?
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Introduction
Adrenal glands are common sites for secondary lesions derived from malignant tumours (lymphoma, melanoma, renal, breast, colon, and bronchopulmonary cancer). Patients with adrenal secondary lesions are typically asymptomatic but 1% may present with adrenal insufficiency as a first manifestation. We report the cases of two males with lung adenocarcinoma, first presented with acute adrenal insufficiency.

Cases presentation
Case 1: LC, 65 years old, was hospitalised for acute asthma, anorexia, severe digestive disorder, weight loss, and hypotension, associated with hypokalaemia. Adrenal insufficiency was confirmed by increased ACTH (344 pg/ml) and low-normal cortisol (6.38 µg/dl). Steroid substitution was started with amelioration of the general status. Abdominal imagery (ultrasonography and CT) revealed enlarged adrenals and a probable secondary hepatic lesion. Liver biopsy suggested a pulmonary adenocarcinoma metastasis, for which chemotherapy was started, with favorable evolution.

Case 2: BV, 57 years old, heavy smoker and drinker, decompensated, after an intervention for Dupuytren retraction, with a primary adrenal insufficiency confirmed by the biological data. Steroid substitution was started with a good initial evolution but after 3 months he stopped the treatment and was hospitalized with adrenal crisis (cortisol <1 µg/dl). Intensive treatment was efficient but the persistence of anorexia, asthma, and inflammatory syndrome suggested a severe underlying cause. Pulmonary radiography showed a right apical lung nodule confirmed by thoraco-abdominal CT, which also revealed bilateral adrenal invasion. Pulmonary biopsy confirmed poorly differentiated adenocarcinoma and chemotheraphy schema was proposed.

Conclusions
The frequency of adrenal metastasis of primary lung cancer increases with disease progression, from 10 to 40%. However, clinical manifestations of adrenal insufficiency are significantly less frequent, probably because a destruction of more than 90% of adrenal cortex is needed for clinical symptoms. Adrenal crisis was, in our two cases, the first symptom of advanced pulmonary cancer, leading to its diagnostic and therapeutic solutions.

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EP82
Marked hypercholesterolemia caused by mitotane adjuvant chemotherapy for adrenocortical carcinoma
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Aim
Mitotane (o,p'-DDD) has been used to treat adrenocortical carcinoma (ACC) for several decades. Mitotane is often given in adjuvant setting after surgical resection of ACC and treatment usually lasts 2–3 years to reduce ACC recurrence. The use of mitotane is associated with multiple adverse effects. We herein report a case of marked hypercholesterolemia in a man receiving mitotane as adjuvant chemotherapy for ACC.

Case
A 64-year-old man was admitted to our Endocrinology Department with the laboratory findings of adrenal insufficiency. Mitotane was started as adjuvant chemotherapy for ACC by the Oncology department. With the usage of 4 g mitotane for 25 days, laboratory results were as follows: ACTH: 298 pg/ml, cortisol: 5.7 μg/dl, DHEAS: 7.3 μg/dl. Hydrocortisone was started as 30 mg/day. As Potassium levels were normal with the hydrocortisone treatment, fludrocortisone was not added to the treatment. Interestingly, the patient developed marked hyper-LDL cholesterolemia at a level of 236 mg/dl following introduction of mitotane. Before the mitotane treatment, LDL level of the patient was 139 mg/dl. After mitotane treatment, total cholesterol was 370 mg/dl, triglyceride was 160 mg/dl, HDL was 94 mg/dl. TSH level of the patient was 1.7 μIU/ml. There was no findings of hypogonadism. There was no medical history of primary familial or secondary hyperlipidaemia. Low dose atorvastatin was started for hyperlipidaemia.

Discussion
In the literature, 21 Cushing’s syndrome patients treated with mitotane exhibited increased cholesterol level (primarily LDL cholesterol) with an average of 68% increase. Mitotane may increase cholesterol by inhibiting the formation of the oxysterol. It may decrease cholesterol catabolism by inhibiting the production of cholesterol oxidase. Mitotane may be able to stimulate the activity of HMG-CoA-reductase strongly enough to significantly increase LDL-cholesterol synthesis.

Conclusion
We recommend careful monitoring of serum cholesterol level following the introduction of mitotane chemotherapy.

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EP83
Fasting during Ramadan in patients with adrenal insufficiency
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Long fasting in patients with adrenal insufficiency could cause hypotension, dehydration or hypoglycaemia. No studies evaluated these risks and there is no recommendations about fasting for these patients. The aim of our study was to evaluate the potential risks of fasting during the month of Ramadan in patients with adrenal insufficiency.

Subjects and methods
It is a cross sectional study that concerned 125 subjects (97 women and 28 men, mean age = 47.1 years), more frequently a primary adrenal insufficiency (27% vs 17%) and secondary (73% vs 83%). The mean level of ACTH was 20.21 ng/l (10–39.7). The average waist circumference was 99.05 cm (range: 80–134). Obesity was found for 46% of patients, overweight for 54% of patients. The response of adrenal insufficiency was HTA for 47.05%, dyslipidaemia for 23.5%, diabetes for 37.65%, and depression for 20.0%. The mean level of ACTH was 20.21 ng/l (10–39.7).

Case
A 47.1 years-old patient was referred to our Medical treatment. Fasting during Ramadan can be complicated especially in aged patients, a primary origin. More studies are needed and a consensus should be established for safe fasting in patients with adrenal insufficiency.

EP84
Awareness of adrenal crisis prevention in long-term steroid users
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Background
Patients taking corticosteroids for immune suppression are vulnerable to adrenal crisis during intercurrent illness or if steroids are stopped abruptly. Although patients on glucocorticoids for adrenal failure are routinely provided with sick day rules, we wished to ascertain whether patients on immunosuppressive steroids are appropriately counselled.

Aim
This study sets out to compare patient awareness of steroid sick day rules in endocrine and non-endocrine patients.

Methods
A 9 point questionnaire to determine knowledge of steroid sick day rules was designed. 92 patients were consecutively recruited from non-endocrine clinics – respiratory (n = 22), rheumatology (n = 24), gastroenterology (n = 20) and nephrology (n = 26). 46 patients were consecutively recruited from the pituitary clinic. All patients completed the questionnaire.

Results
Endocrine patients exhibited better steroid awareness; they were more likely to double their steroid dose when ill (76.1% vs 6.5%), to obtain parenteral steroid during vomiting (82.6% vs 27.1%), and during surgery (80.0% vs 30.4%), and were aware of the need to carry a medical alert bracelet or a steroid-aware card (82.6% vs 20.7%). P < 0.001 for all. However the endocrine patients were at par with the non-endocrine ones in terms of knowing the need to inform their doctor of being on steroid (91.3% vs 88.0%).

Conclusion
Endocrine patients exhibited a significantly greater knowledge of precautions for steroid use. The data does highlight the lack of patient awareness of the sick day rules in patients on immunosuppressive therapy for non-endocrine conditions. Endocrinologist could assist colleagues in other specialties in awareness of steroid sick day rules.

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EP85
Subclinical Cushing’s syndrome: report of 17 cases
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Introduction
Subclinical Cushing’s syndrome refers to autonomous cortisol secretion in patients who do not have the typical signs and symptoms of hypercortisolism. This study was undertaken to describe clinical, biological and radiological features of this disease and to evaluate the clinical outcome after surgical and medical treatment.

Methods
Retrospective study conducted over a period of 12 years and including 17 patients hospitalized in our department of endocrinology for subclinical Cushing’s syndrome.

Results
The average age of our patients was 58.94 years (range: 38–77) with a sex ratio (M/F) of 1:1.2. The average waist circumference was 99.05 cm (range: 80–134). Obesity was found for 46% of patients, overweight for 54% of patients. The response of dexamethasone suppression test (2 mg) was altered for all patients. Urinary free cortisol was dosed for four patients (23.5%), normal in three cases (75%) and high in one case (25%). The mean level of ACTH was 20.21 ng/l (10–39.7). The adrenal CT showed an unilateral adenoma for 82%, bilateral adrenal hyperplasia for 12% and two right adrenal adenoma for 6% of cases. The repercussions of subclinical Cushing’s syndrome were HTA for 47.05%, dyslipidaemia for 23.5%.

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A single-centre 10-years experience with pasireotide in Cushing’s disease: patients characteristics and outcome

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Introduction
Pasireotide is the first pituitary-directed drug approved for Cushing’s disease (CD). We report our 10-years experience with pasireotide in CD reaving and analysing data about all the patients treated with pasireotide at our referral centre both in randomised trials and in clinical practice.

Patients and methods
Twenty active CD patients were treated. Fourteen patients were treated with pasireotide in randomised trials and six patients were treated with pasireotide s.c. (Signifor; Novartis AG) in clinical practice. The mean treatment duration was 20.5 months (median 9 months; range, 3–72 months). The mean daily s.c. dose was 1333 μg (range, 1200–1800 μg) at the beginning of treatment as well as 1366 μg at last follow-up (range, 600–2400 μg).

Results
Urinary free cortisol (UFC) levels mean percentage change (+/- s.e.) at last follow-up was −40.4% (+/-35.1%; range, 2–92%; median reduction 33.3%) with a normalisation rate of 50% (10/20). UFC normalisation occurred by months 1–3 in the majority of patients (8/10; 80%). Ten patients achieved sustained normalised late night salivary cortisol (LNSC) levels during treatment. LNSC normalisation was associated with UFC normalisation (7/10 patients). Serum cortisol and plasma ACTH significantly decreased from baseline to last follow-up. Body weight decrease and blood pressure improvement during treatment were independent from UFC response. Glucose profile worsening was observed in all the patients except one. The frequency of diabetes increased from 40% (8/20) at baseline to 85% (17/20) at last follow-up requiring to start medical treatment only in a half of patients (8/17).

Conclusions
Pasireotide treatment was associated with sustained biochemical and clinical benefit in about 50% of CD patients. Glucose profile alterations are a frequent complication of pasireotide treatment however this adverse event seems to be easy to manage with diet and lifestyle intervention in almost half of patients.

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EP99
Low DHEAS: a sensitive and specific screening test for the detection of subclinical hypercortisolism in adrenal incidentalomas
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Subclinical hypercortisolism (SH) occurs in 5–30% of incidentally-detected adrenal adenomas (AIs). Common screening tests for ACTH-independent hypercortisolism have significant false positive rates, mandating further investigations that are both time and resource intensive. We investigated whether a low basal DHEAS level is a sensitive and specific screening test for the detection/exclusion of SH in patients with newly-diagnosed AI. We recruited 185 consecutive patients with AI referred to our clinic between 2006 and 2013 were screened for clinical and biochemical evidence of adrenal medullary and cortical (1 mg dexamethasone suppression test, 24 h urinary free cortisol (UFC), serum DHEAS, plasma renin and aldosterone) hyperfunction. All positive dexamethasone suppression (> 1.8 μg/dl) and UFC (> upper limit of reference range) results were further investigated, and we diagnosed SH when at least two of the following criteria were met: raised UFC, raised midnight serum cortisol, 48 h dexamethasone suppression test cortisol > 1.8 μg/dl (50 mmol/l). Plasma ACTH was <10 pg/ml (2.2 pmol/l) in all patients with SH. At presentation, 29 patients (16%) were diagnosed with SH. We calculated an age-and gender-specific DHEAS ratio (derived by dividing measured DHEAS by the lower limit of the respective reference range) for all patients in the cohort and found that a ratio ≤ 1.12 was a sensitive (100%) and specific (91.9%) screening test for the diagnosis of SH. In comparison, a cortisol level after a 1 mg dexamethasone suppression test of 1.9 μg/dl (53 nmol/l) was a sensitive (100%) screening test for SH, but had lower specificity (82.9%). 24 h UFC lacked sensitivity (69%) and specificity (68%). A single basal measurement of DHEAS offers comparable sensitivity and greater specificity to the existing gold-standard 1 mg dexamethasone suppression test for the detection of SH in patients with AIs.

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EP100
Ultrasound importance in adrenal incidentalomas diagnosis and management
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Background
Adrenal incidentalomas are detected in about 0.1% of general health screening with ultrasound, in 0.4–1.9% among patients evaluated for nonendocrineologic complaints, in ~4.4% among patients who have a previous cancer diagnosis. Majority are benign, but careful evaluation is warranted to rule out carcinoma and functional adenomas.

Aim
The purpose of presenting these cases is to highlight the importance of ultrasound examination in diagnosis and management of adrenal incidentalomas.

Materials and methods
We have prescribed six patients presenting in our clinic during a 3-year period, which resulted with adrenal incidentaloma in abdominal ultrasound. They underwent specific blood tests, depending on the clinical situation.

Results
Case 1 was a 41-year old male, presenting with hyperglicemia found to have Conns’ syndrome with aldosterone producing adenoma on routine ultrasound. Case 2 was a 21-year old boy, who had pheochromocytoma misdiagnosed as anxiety disorders. Case 3 was a 49-year old female, presenting amenorrhoea which was mistaken as menopause, and minimal hirsutism which was mistaken as postmenopausal hirsutism. She resulted with adrenal androgen secreting adenocortical carcinoma. Case 4 was a 59-year old hypertensive male, presenting with fever had pheochromocytoma with catecholamine excess, producing fever. Case 5 was isolated adrenal tuberculosis, who presented with chronic diarrhea. Case 6 was a 43-year old female, presenting with drug-resistant hypertension and diabetes, found to have Cushing’s syndrome.

Conclusion
Adrenal incidentalomas are common, most are non-secreting adenomas. When a hormonal disorder is suspected clinically, specific blood tests for Cushing, Conn and/or pheochromocytoma are indicated.

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EP98
Long-term outcome from unilateral adrenalectomy in patients with primary aldosteronism
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Primary aldosteronism (PA) is an important cause of hypertension which confers significant cardiometabolic risk. In approximately half of cases, the cause is a surgically resectable unilateral aldosterone-producing adrenal adenoma, making PA the most common potentially curable form of hypertension. Despite this, long-term data on surgical outcomes that could be used to guide discussions with patients are sparse. Here, we report on clinical outcomes several years post-adrenalectomy in those patients from our prospectively studied cohort who underwent surgery. Of 120 consecutive patients investigated for PA, 51 underwent laparoscopic-assisted adrenalectomy. Blood pressure, number of antihypertensive medications, and serum potassium were recorded before adrenalectomy, and at the time of most recent follow-up. Recumbent renin and aldosterone were measured ≥3 months after surgery, to determine if PA had been biochemically cured. This was performed in the absence of interfering antihypertensive medication, and with oral potassium supplementation given as necessary.

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The cohort consisted of 31 males and 20 females, median age 54 (range 30–83). Median duration of follow up was 48 months (range 3–154). Median pre-operative blood pressure (on medication) was 160/95 (range 120/80–250/150). Overall, blood pressure significantly improved post-operatively, to a median of 130/80 (range 110/70–160/93, P < 0.0001). Median serum potassium level increased from 3.2 mmol/l pre-operatively (range 2.3–4.7) to 4.4 mmol/l post-operatively (range 3.3–5.3, P < 0.0001). Median number of antihypertensive medications used improved from median 3 pre-operatively to median 1 post-operatively (P < 0.0001). 3/51 patients (5.9%) did not achieve any improvement in blood pressure post-operatively; however, histological examination of these patients’ removed adrenal glands confirmed the presence of fully excised, typical CNT’s adenomas in each case.

Laparoscopic-assisted unilateral adrenalectomy provides excellent long term improvements in blood pressure control, polypharmacy, and hypokalaemia. These data may help inform discussions with patients about possible surgical outcomes.

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EP93

Phaeochromocytoma-the Mater hospital experience over the past two decades
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Phaeochromocytoma is a rare neuroendocrine tumour. Incidence has been quoted as two to eight cases per million people. This study reviews all cases of surgically resected phaeochromocytoma in a large tertiary referral centre since 1996 with particular focus on preoperative care. 22 patients were diagnosed with phaeochromocytoma with average age at diagnosis of 47 years. 13.6% (n = 3) of patients had malignant phaeochromocytoma. Two patients had confirmed neurofibromatosis Type 1. The remaining cases were deemed sporadic and are awaiting genetic analysis. In terms of pre-operative optimisation, medical stabilisation is required to prevent adverse surgical outcomes. 22 patients were diagnosed with phaeochromocytoma with average age at diagnosis of 47 years. 13.6% (n = 3) of patients had malignant phaeochromocytoma. Two patients had confirmed neurofibromatosis Type 1. The remaining cases were deemed sporadic and are awaiting genetic analysis. In terms of pre-operative optimisation, medical stabilisation is required to prevent adverse surgical outcomes.

In this study 15/10 mm/Hg. The mean heartrate pre-operatively was 74 bpm. Of the 22 patients that underwent surgical resection, 81.8% of patients (n=18) required ITU/HDU care post-op with an average length of stay of 3.1 ± 1.6 days. 50% (n = 11) required inotropic support post-op for an average of 1.9 ± 1.1 days. In terms of immediate post-op complications, hypotension was the most common. One patient (known catecholamine induced cardiomyopathy) developed a cardiac arrest during anaesthetic induction. There was one case of post op hypertension requiring nitrate infusion. Mortality related to surgery was nil. One patient has died secondary to complications of metastatic phaeochromocytoma, the other patient died of an unrelated condition. In the 22 cases described, each presented a unique set of management challenges. This report showed that once diagnosed, intensive medical stabilisation is required to prevent adverse surgical outcomes.

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EP94

Combined effects of sirolimus and mitotane in the inhibition of growth in human adrenocortical carcinoma cells
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Adrenocortical cancer (ACC) is a rare cancer with poor prognosis and scant treatment options. Mitotane alone, or in combination with cytotoxic chemotherapy, represents the referral current treatment for patients with intractable ACC. Recent studies have shown that mTOR inhibitors suppress growth of ACC cells. This study aimed at evaluating the effects of mitotane in combination with mTOR inhibitors. In H295 and SW13 cells we tested the effects of a 6 day treatment with increasing doses of mitotane in the presence or absence of selected doses of sirolimus on cell proliferation as measured by the total DNA content. The tested doses of mitotane ranged between 10−7–10−5 M in both H295 and SW13 cells, sirolimus was tested at concentrations of 5×10−5 and 10−4 M in H295 and 5×10−11 and 10−10 M in SW13. In H295,mitotane significantly inhibited cell proliferation at all concentrations tested, with an IC50 of 4.5×10−5 M and a maximal inhibition of 87% as compared with vehicle-treated controls (P < 0.001). In SW13, mitotane significantly inhibited cell proliferation at concentrations higher than 2.5×10−8 M, with an IC50 of 1.6×10−7 M and a maximal inhibition of 81% as compared with vehicle-treated controls (P < 0.001). In both H295 and SW13 mitotane significantly inhibited cell proliferation at both concentrations tested and when combined with mitotane, it showed statistically significant additive effects. This additivity was observed only with low mitotane doses (between 10−7 and 5×10−8 M). Using mitotane doses higher than 5×10−4 M the cell proliferation inhibition was already nearly maximal and no significant additive effects could be observed. The current study demonstrates that sirolimus has additive antiproliferative effects when combined with low mitotane doses. These doses correspond to concentrations lower than the therapeutic range of mitotane. If this effect can also be achieved in vivo our data suggest that the addition of sirolimus to mitotane might be useful in ACC patients when the therapeutic range of mitotane is not reached.

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EP95

Linear growth and endocrine function in patients with ataxia telangiectasia; a cohort of 13 patients in Qatar
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Introduction
Ataxia telangiectasia (AT) is a rare, genetic, primary immune deficiency disease characterised by immunodeficiency and neurological manifestations, with increased tendency to infection, malignancy, and autoimmune diseases. Both growth delay and endocrine abnormalities are occasionally reported in these patients. Aim To study linear growth in relation to endocrine and immune functions in a cohort of children with AT. Patients and methods We studied growth parameters (height (Ht), weight, BMI and measured the HsDS of 13 patients (age 7.7±3.5 years) with AT in relation to their mid-parental HsDS. We measured their biochemical (serum calcium (Ca), phosphorus (PO4), alkaline phosphatase (ALP), alanine transerase (ALT), ferritin, creatinine and albumin), endocrine (free thyroxine (FT4), TSH, IGF1, 8 AM cortisol) and immune functions (IgG, IgM and IgA antibodies). Growth data were correlated to hormonal and immune data.

Results
Presented in table.

Steroids, development and paediatric endocrinology EP96

Linear growth and endocrine function in patients with ataxia
telangiectasia; a cohort of 13 patients in Qatar
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Introduction
Ataxia telangiectasia (AT) is a rare, genetic, primary immune deficiency disease characterised by immunodeficiency and neurological manifestations, with increased tendency to infection, malignancy, and autoimmune diseases. Both growth delay and endocrine abnormalities are occasionally reported in these patients. Aim To study linear growth in relation to endocrine and immune functions in a cohort of children with AT. Patients and methods We studied growth parameters (height (Ht), weight, BMI and measured the HsDS of 13 patients (age 7.7±3.5 years) with AT in relation to their mid-parental HsDS. We measured their biochemical (serum calcium (Ca), phosphorus (PO4), alkaline phosphatase (ALP), alanine transerase (ALT), ferritin, creatinine and albumin), endocrine (free thyroxine (FT4), TSH, IGF1, 8 AM cortisol) and immune functions (IgG, IgM and IgA antibodies). Growth data were correlated to hormonal and immune data.

Results
Presented in table.

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Summary
Patients with AT had high prevalence of growth delay and endocrine dysfunction in the form of low IGF1 clinical and subclinical hypothyroidism and hypogonadism. Early diagnosis and management of these endocrinopathies is important or improving the prognosis of the disease.

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EP96

Abstract withdrawn.

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EP97

Unusual presentation of the apparent mineralocorticoid excess, triggered by mild Cushing's disease in an adult
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Introduction
The syndrome of apparent mineralocorticoid excess (AME), a genetic disorder, resembles findings similar to those in primary aldosteronism, but aldosterone levels are low. AME is due to deficiency in the 11-beta-hydroxysteroid-dehydrogenase-enzyme-type-2 isoform (11-beta-HSD2), which normally converts cortisol to cortisone to prevent its mineralocorticoid activity at the aldosterone-sensitive sites. The deficiency in 11-beta-HSD2 leads to marked elevation in net mineralocorticoid activity caused by unconverted cortisol.

Case report
50-years-old woman was hospitalised after collapse. She had had arterial hypertension for 10 years (bisoprolol 5 mg/day, perindopril/indapamide 8/2.5 mg/day). At the presentation she was hypotensive 96/64 mmHg, mildly Cushingoid, BMI 28 kg/m². Initial laboratory results: s-K 2.44 mmol/l, spot u-K 56.44 and 61.27 nmol/l, free cortison two-times undetectable. Spironolactone 60 mg/day was introduced. With the dose of 150 mg/day the patient is normokalaemic, and aldosterone sensitive sites. The deficiency in 11-beta-HSD2 leads to marked elevation in net mineralocorticoid activity caused by unconverted cortisol.

Conclusion
11-beta-HSD2 deficiency is a rare cause of hypertension and hypokalaemia. Presented case report is of special interest showing that mild Cushing’s disease has unmasked the underlying enzyme deficiency. Genetic testing is in progress. Transphenoidal microadenomectomy is planned.

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EP98

Evaluation of β-oestradiol induced DNA damage in the leukocytes of young, elderly and Alzheimer's disease patients in the comet assay
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Oestrogen has very complex effects on the CNS. It protects neurons from noxious effects of β amyloid in vitro, ameliorates the cerebral metabolism and increases the level of acetylcholine in the basal forebrain and hippocampus. Its beneficial impact in Alzheimer disease may be attributed in part to its antioxidant activity. On the other hand, it has been demonstrated that oestrogens may exhibit genotoxic effects, especially at elevated tissue concentrations. Therefore, the aim of the present investigation was to determine whether oestradiol induces DNA damage in whole blood leukocytes from healthy young females and males, healthy elderly females and males and females and males with Alzheimer disease. All experiments were performed using the alkaline version of the Comet assay (single cell gel electrophoresis). Cell viability was determined by Trypan blue exclusion assay. A significant increase of DNA migration in the Comet assay was observed in leukocytes of all treated groups (young and elderly females, young and elderly males, females and males with Alzheimer disease) at all concentrations of oestradiol (50, 100 and 250 µM) used in this investigation. In all experiments the cell viability was over 80%. Therefore, it can be concluded that leukocytes are sensitive to oestradiol in the Comet assay regardless of gender, age and health condition of examined subjects.


EP99

Serum alanine aminotransferase and γ-glutamyltranspeptidase activities: new markers for polycystic ovary syndrome
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Objective
Polycystic ovary syndrome (PCOS) is associated with insulin resistance, central obesity and dyslipidaemia. Furthermore, abnormal aminotransferase activity is common in women with polycystic ovary syndrome. The aim of this study is to assess the γ-glutamyltranspeptidase (GGT) and alanine aminotransferase (ALT) levels in women with PCOS in whom non-alcoholic fatty liver disease was excluded by history, serum testing and abdominal ultrasoundography.

Study design
Present work is included 135 consecutive outpatient between January and July 2006. Ninety patients for the diagnosis of PCOS and 45 age-matched healthy subjects in the control group. Women with PCOS were separated into two groups. Group A were treated with 0.035 mg of Ethinyl Oestradiol and 2 mg of cyproterone acetate for 6 months. Group B did not take any drug. Serum levels of ALT, as-part of aminotransferase (AST), GGT, alkaline phosphatase (ALP), lipid and glucose metabolism parameters were measured on the 6th month of treatment.

Results
The plasma levels of both ALT and GGT were significantly higher in the subjects with PCOS (total) compared to the controls. Serum GGT levels were significantly higher in the group A and B than in controls, whereas no difference was found between group A and B. On the other hand group B had significantly higher ALT levels than in controls. However, no differences in ALT levels were found between group A and controls.

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Conclusions
The ALT and/or GGT levels are important in the pathogenesis of PCOS and that hepatic enzymes may be useful additional measures in identifying women at high risk of metabolic syndrome. 
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**EP101**

**Interrelation between level of knowledge and type 1 diabetes mellitus compensation degree in children and adolescents**

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**Aim**

To assess level of knowledge and compensation degree in children and adolescents with type 1 diabetes mellitus in “Type 1 Diabetes School”.

**Materials and methods**

The 5-day training course was conducted in “Type 1 Diabetes School” at the Center for the Scientific and Clinical Study of Endocrinology. The training was conducted by means of a structured program containing all appropriate sections. Before and after training all participants were tested with a questionnaire containing 30 key questions for self-control. On the basis of the findings children and adolescents with type 1 diabetes mellitus were divided into groups. 54 of 80 children and 38 of 57 adolescents were preliminary trained, 26 children and 19 adolescents got no training. DS5 Glycomat (USA) was used to measure HbA1c by means of high pH anion-exchange liquid chromatography. Certified by the National Glycohaemoglobin Standardization Program this method became the reference one. It helps demonstrate the predicting role of HbA1c level as a criterion for assessment of chronic glycaemia and achievement of therapy targets in children and adolescents with type 1 diabetes mellitus.

**Results and discussion**

Frequency of target HbA1c level (≤7.5%) achievement in the trained patients was 68%. Among children who got no preliminary training target HbA1c level was found in 12%. Among trained adolescents 58% achieved compensation. The target HbA1c level was found in 11% of adolescents who got no training.

**Conclusions**

Frequency of target HbA1c level (≤7.5%) achievement was found in 68% of children with type 1 diabetes mellitus having received preliminary training at ‘Diabetes School’ to be significantly higher (P < 0.001) than the one in the group of patients who got no preliminary training (12%). Among adolescents target HbA1c level achievement was observed in 58% of the trained patients to be significantly higher (P < 0.001) as compared with those who got no preliminary training (11%). Better compensation and higher frequency of target HbA1c level achievement in children as compared with those among adolescents confirms the role of family in the type 1 diabetes mellitus control.

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**EP102**

**Influence of ecologically adverse factors on physical and sexual development of children living in the Aral Sea area**

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Drying of the Aral Sea resulted in serious problems including pollution of air, water (mineralization of clear water) and soil which in its turn caused rise in various somatic diseases in population and produced a negative effect on health of children and adolescents.

**Purpose**

To study the influence of ecologically adverse factors on physical and sexual development of children of the Aral Sea area.

**Materials and methods**

To estimate physical and sexual development of adolescents of the Aral Sea area an epidemiological survey was carried out in 2008 using a method of random sampling considering age and sex. The study group comprised 1120 children (600 girls and 620 boys) aged 12 to 16. The study included anthropometry (coefficient of standard deviations SDS), BMI, estimation of sexual development (according to Tanner), USI of the small pelvis organs.

**Results**

Of 1220 children examined, stature was found in 143 (11.7%) and weight deficiency in 67%. It should be noted that 85% of children were registered at the dispensary for anemia. The ratio of occurrence of stunting between boys and girls made 2:1. Of 620 boys examined stunting was found in 14.3%, sexual development retardation in 20% of boys, hypogonadism in 3%, obesity in 1.7%, microgenit in 2.5%, unilateral cryptorchism in 1.2%, other boys had normal for age puberty development. Of 600 girls examined stunting was revealed in 7.3%, abnormal puberty in 2.8%, retardation of sexual development in 12.8%, late menarche in 12.1% and primary amenorrhea in 4.3% of girls. Thus, the results obtained suggest on direct influence of adverse ecological factors (pollution of air, water, soil) of the Aral Sea area on health of children being confirmed with frequency of stunting (11.7%) in children and sexual development disorders revealed.

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Kisspeptin is a neuropeptide secreted in anteroventral-periventricular and arcuate hypothalamic nuclei involved pubertal onset and in other functions of adult life. Kisspeptin levels are sex dependent, so they are higher in prepubertal girls and in adult women compared to age-matched male. This sex-related pattern has been reported in adult obesity, but few data are reported in childhood obesity. In order to evaluate correlations between metabolic status and kisspeptin, we studied Kisspeptin levels in a population of 27 prepubertal children (13 males) aged 5–12 years, classified as overweight (n = 5) or obese (n = 22) according to Cole’s criteria. Eight normal weight children, aged 6–12 years, were enrolled as controls. Several metabolic parameters were evaluated: glucose and insulin levels after oral glucose load, total, LDL- and HDL-cholesterol, triglycerides, uric acid, total proteins, C Reactive Protein. Leptin was evaluated using ELISA method (DRG Instruments GmbH, Germany). In order to evaluate kisspeptin levels, morning blood samples were collected; after acidification, peptides were extracted in a C-18 SEP-Column (Phenomenex, Inc., USA). The eluted samples were evaporated and stored at − 80 °C until assayed. Kisspeptin (pg/ml) was measured using the RIA kit KissR (61-121)-Amide-Metastin (1-54)-NH2 (Phoenix Pharmaceuticals, Burlingame, USA). We did not find significant differences between obese and normal weight children (mean ± S.E.M: 20.1 ± 1.96 and 20.7 ± 0.68 pg/ml, respectively) and between males and females obese children (19.05 ± 3.39 and 20.9 ± 2.49 pg/ml). Kisspeptin levels did not correlate with SDS BMI, HOMA index and Insulin peak levels after glucose load. As expected, Leptin levels were higher in obese children than in controls (20.41 ± 2.84 and 4.21 ± 2 ng/ml, respectively), while showed a significant correlation with Kisspeptin levels in normal children (R² = 0.12, P value = 0.46), but not in obese (R² = 0.03, P value = 0.6). These preliminary data suggest that Kisspeptin could play a role in metabolic status and could be regarded as metabolic modulator and not only a regulator of pituitary gonadal axis. DOI: 10.1530/endoabs.37.EP103

Kisspeptin hormone levels in girls and adolescent girls
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Kisspeptin (formerly known as metasin) is a neuropeptide, has an important role in initiating secretion of gonadotropin-releasing hormone at puberty. Kisspeptin hormone levels disorders cause hypogonadalism or premature sexual development and sterility.

Aims
The study was undertaken to research the kisspeptin level in healthy girls and adolescent girls and in girls and adolescents with gynaecological and endocrine disorders.

Patients and methods
Serum kisspeptin levels were determined in 100 children and adolescents (aged 0.7–18 years). The healthy children were 12, children with precocious puberty (central precocious puberty CPP and premature isolated thelarche PIT) – 11, healthy adolescents – 30, girls with amenorrhea – 23, patients with polycystic ovary syndrome (PCOS) – nine and pregnant adolescent girls – 15. The concentration of kisspeptin was measured using Kisspeptin-10 and competitive enzyme immunoassay. Results were analyzed using two-way ANOVA. Data are expressed as median, P value of < 0.05 was considered statistically significant. Results
The investigation shows that healthy and pregnant adolescent girls had kisspeptin median levels 0.03 ng/ml. Among the girls with amenorrhea and PCOS kisspeptin levels were lower 0.01 ng/ml (P = 0.014). Serum kisspeptin levels were significantly higher in children with CPP and PIT and adolescent girls with PCOS than in control group (0.08 and 0.3 vs 0.03 ng/ml, P = 0.012 and P < 0.001).

Conclusion
Kisspeptin levels were various in healthy children, adolescents and girls with amenorrhea, PCOS, children with central precocious puberty and PIT. In this study, we demonstrated that serum kisspeptin levels were not different in healthy adolescents and pregnant adolescent girls. In this study, we demonstrated that

EP105
Clinical and endocrine features Hashimoto thyroiditis in children and adolescents
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Introduction
Hashimoto’s thyroiditis (HT) is the most common autoimmune thyroid disease and the most common cause of euthyroid goitre and acquired hypothyroidism in childhood.

Objective
To describe the clinical manifestations, course and outcome of HT in children and adolescents.

Method
The study included 43 patients with HT, aged 3–16 years, mean age 12.5 years, 36-girls, seven boys; 15 (35%) prepubertal, 28 (65%) pubertal, monitored on average of 4.9 years.

Results
Goitre is the most common symptom of HT, recorded in 19 (44.3%), and during follow-up in 31 (72%) of the children. In 17 (49.5%) were diffuse goitre, and in 15 (34.4%) children was isolated symptom. Goitre was recorded in 14 (73.7%) girls and 5 (21.3%) boys. Other clinical symptoms HT are: anaemia in seven patients (16.2%), fatigue in 5 (11.8%), increased appetite in 4 (9.7%), obtaining in TM (7.0%), growth retardation in 2 children (4.7%) and irregular menstrual cycle in 5 (23.8%) out of 21 pubertal girls. Hypothyroidism is initially recorded in 7 (16.3%), and during follow-up the euthyroid state in 25 patients (58.1%). A positive family history of autoimmune thyroid disease had 18 (41.9%) children, of which 13 (72.2%) demonstrated hypothyroidism. In 12 (27.8%) children were identified: DMT1 in six children, vitiligo in two, M.Coelius in three, and M.Gravis in one child.

Conclusion
HT is five times more common among girls. The most common clinical symptom HT is a diffuse goitre, and hypothyroidism is recorded in 42%. The frequency of positive family history of autoimmune thyroid disease is high in children with HT, which increases the risk of developing hypothyroidism. As almost one-third of children with HT manifested and other autoimmune diseases, clinical follow-up involves the search for them.

EP106
Neonatal screening for hypothyroidism in Romania
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Introduction
Neonatal screening is an effective method for early detection of congenital hypothyroidism, a disorder that requires the prompt initiation of the treatment, in order to prevent the subsequent neuropsychiatric impairments. Neonatal screening for hypothyroidism in Romania was initiated as a pilot project in 1979, has been expanded since 2002, and is currently conducted through the National Health Program funded by the Ministry of Health.

Objective
To assess the current state of hypothyroidism screening and management in Romania and determine the incidence of hypothyroidism at birth in 2013.

Material and methods
We analysed data reported to the Implementation Unit of Health Programs in 2013 by the four regional centres (Bucharest, Cluj, Iasi and Timisoara) and the parameters registered in the Hypothyroidism National Registry (in Bucharest and Iasi). The confirmed cases were treated and monitored by the endocrinology network. All the newborns were investigated by the ‘dry spot’ method; blood samples were collected from the heels. TSH levels were assessed by immunofluorimetric
method in three regional centres and by Elisa technique in the fourth. The diagnosis was locally confirmed by TSH, T4 and free-T4 levels in patients serum.

**Results**

In 2013, 92.76% of newborns were screened for hypothyroidism. 96 patients (0.07%) were found positive, when a neo-TSH cut-off value of 15 mU/L was used; in 41 newborns (0.03%) congenital hypothyroidism was confirmed. The family refused the diagnosis investigations in three patients (0.002%). The hypothyroidism incidence in this study is 1/3409 infants.

**Conclusion**

The incidence of congenital hypothyroidism in Romania is within the limits reported in literature. We attempt to increase the number of the newborns tested for hypothyroidism by raising awareness about screening benefit among the families. Taking into account the false positive cases, we estimate that ongoing studies will enable the increase of the neo-TSH cut-off value at 17 mU/L.

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**EP107**

Paediatric hypothyroidism: effect of thyroxin replacement therapy on growth hormone secretion and linear growth velocity

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Thyroid gland secretes thyroid hormones, which play a critical role in growth, differentiation, reproduction and metabolism, whereas hypothyroidism in children is associated with short stature and normalisation of thyroid function with thyroxin replacement therapy increases linear growth velocity (LGV). In stimulating LGV, thyroxin may have its direct effects on bone cells or it may affect LGV through its effect on growth hormone (GH) secretion. The present study attempted to examine the effect of thyroxin replacement therapy on LGV in hypothyroid short children, its effect on GH secretion and the stage of puberty at which thyroxin replacement therapy could be more effective in influencing LGV.

Blood samples were obtained and plasma TSH, T4, T3, GH and IGF-I were determined using specific assay systems. Data were analysed using Student’s t-test and ANOVA. Twenty hypothyroid children (ten boys and ten girls) diagnosed on the basis of lower plasma levels of T4 and T3 and higher plasma concentrations of TSH, were given varying doses of thyroxin (16.6–150 µg/day for 12–36 months) administered orally at different ages (8–16 months) and stages (early, mid and late) of puberty development. Following replacement therapy, children grew at a greater rate at higher doses of thyroxin. In addition, thyroxin replacement at early puberty in girls and mid puberty in boys caused higher increases in LGV. The concentrations of GH and IGF-I increased significantly after treatment of hypothyroid patients with thyroxin. In conclusion, the present study demonstrates that hypothyroid children grow at a greater rate at higher doses of thyroxin and that thyroxin replacement therapy at early puberty in girls and at mid puberty in boys causes higher increases in LGV. In addition, the current investigation indicates that increases in LGV following thyroxin replacement therapy are secondary to GH and subsequent IGF-I secretion.

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**EP108**

Evolution of the signs of true precocious puberty under suppressive treatment by LH RH analogues in girls

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**Introduction**

Impact of suppressive therapy with LH RH analogues is more stop the premature pubertal development, reduce the acceleration of bone maturation that compromises the final size and avoid psychological disturbances caused by hormonal imbalance.

**Aim**

To study the effects of treatment on pubertal development, bone maturation and evolution of the size during and at the end of treatment and final height in 20 patients with central precocious puberty treated by triptorelin.

**Subjects and methods**

15 children (chronological age at diagnosis: 8±1.8 years) at the end of treatment (11±0.1 years) and the final size (15.9±2.5 years) were treated for a central precocious puberty. The selection criteria for this study were treatment of central precocious puberty by Decapeptyl during 2 years or more. We assessed pubertal status, size and bone maturation at the beginning and the final size after stop taking treatment.

**Results**

At the beginning of treatment, pubertal development was S3 (S2–S4, size +2.1±0.8 DS/TC) and AO/10.5±0.8 years. Under treatment, breast development decreased and bone maturation decelerated. The mean final height was 158.2±6.6 cm; –1.5±0.1 DS/TC.

**Discussion and conclusion**

Treatment of central precocious puberty by GnRH agonists stabilizes or regressed pubertal development and decreases bone maturation rate. However when indicated late, the prognosis size is not satisfactory.

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**EP109**

DHEA and its metabolites – daily profile

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**Introduction**

DHEA is a well-known neurosteroid. Its plasmatic level is reduced with ageing in most individuals. A non-negligible portion of DHEA is hydroxylated at C7 and C16 to 7α-, 7β- and 16α- and 16β-hydroxy derivatives. A part of the antiglucocorticoid function of DHEA has been described to its 7-oxygenated metabolites, namely 7α-hydroxy-DHEA. Due its anti-glucocorticoid action it is also considered a factor in fat deposition processes. Thus, we were interested in examining daily profiles of DHEA and its metabolites, as well as possible associations with daily variation of hormones associated with food intake.

**Description of methods**

8 women of reproductive age with normal BMI were given five standardised meals, and their hormonal milieu was determined during the course of the day. Plasma from 12 withdrawals was analysed for DHEA and its 7- and 16-hydroxylated metabolites. The Ethical Committee of the Institute of Endocrinology approved the study.

**Results**

Free DHEA showed a small but significant decrease after lunch and dinner, whereas conjugated DHEA decreased only after dinner. Androstenediol decreased after lunch, but other changes were not significantly influenced by meals. 7α-hydroxy-DHEA and 3β,7α,17β-hydroxyandrostenediol followed the profile of DHEA, but 7β-isomer, 7α- and 16β-hydroxy derivatives showed an increase at 2200–2300 h, which, however, was significant only for free and conjugated DHEA, 7β-hydroxy-DHEA and 16α-hydroxy-DHEA.

**Conclusion**

The daily profile of DHEA levels shows a decrease throughout the day from the highest values in the morning value, with additional significant decreases after main meals. Only some hydroxylated metabolites and conjugated derivatives show a similar profile.

**Disclosure**

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**EP110**

ACTH secretory tests in children in the course of ACTH secretory tests in children in the course of 24 observations

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**Introduction**

The inflammatories background processes, and infiltrating tumour of the pituitary stalk are rare. They are a heterogeneous group of lesions responsible of partial or global hypopituitarism.
Aim
Search for thickening of the pituitary stalk aetiologies and specify the clinical aspects.

Population methodology
This is a retrospective study of 24 patients with thickening of the pituitary stalk. All patients benefited from a clinical, biological and radiological exploration.

Results
A female predominance (17 women) with four paediatric cases are observed. The average age is 30 years (7–48). MRI was performed for hypopituitarism dissociated (n: 19); diabetes insipidus (n: 4) and early puberty (n: 1). The attainment of the stem is associated with a hyperprolactinaemia in 15 cases (62%, 4%). Thyrotropin insufficiency in 16 cases (66.6%), gonadotropin insufficiency in ten cases (41.6%), corticotropic insufficiency in five cases (20.8%), somatotropin insufficiency in four cases (16.6%) and central diabetes insipidus in four cases (16.6%). The aetiologic investigation led to the diagnosis of sellar metastasis in three cases (12.5%), neurosarcoidosis in 15 cases (62.4%), autoimmune hypophysitis in two cases (8.3%) and germinoma in one child (4.16%). Finally the aetiological investigation was negative in the remaining three cases (12.5%, two children).

Discussion and conclusion
The causes of thickening of the pituitary stalk are varied. They must be some thoroughly researched and monitored in idiopathic forms. La frequency of pituitary involvement encouraged to regular hormonal evaluations.

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EP111
The beast behind the dwarf
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Abnormalities of growth are one of the most common reasons for the paediatric–endocrinology consultations. It’s an obvious manifestation with countless possible causes behind, and sometimes we can have unexpected diagnosis. Case presentation was investigated the case of a 4 years old girl, born at term, naturally, SGA; birth weight = 1950g, who presented in the Endocrinology Department for short stature. Clinical evaluation: 89.5 cm (–4 DS), 11 kg (–2.5 DS), discrete ocular asymmetry. Blood test: anaemia, decreased IGF-1, normal adrenal and thyroid function, normal karyotype, normal thoracic X-ray and abdominal ultrasound. Moreover, the first day of admission we noted polyuria and polydipsia not reported by mother: ingestion 3750 ml/24h excretion 3950 ml/24h. Afterwards, biochemical tests confirmed the suspicion of diabetes insipidus. Ophthalmologic exam – important papillary oedema. MRI revealed an expansive mass with contrast enhancement located in posterior fossa. An angio MRI and a biopsy were performed and established the final diagnosis: histiocytosis. Even if in our patient’s case, the short stature and diabetes insipidus, were considered initially easy to manage and benign, the histiocytosis was found to be an unexpected and unpleasant diagnosis which involves more aggressive treatment and complications.

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EP112
Final size of turner patients: about 40 patients
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Introduction
The growth failure constant in turner syndrome is responsible for a spontaneous reduction in adult height with an average of 143 cm. Treatment with growth hormone has enhanced the stature prognosis.

Aim
Studying the final size of turner patients who have completed their growth.

Population methodology
40 patients became adult patients were assessed on linear growth. The following factors were studied: The age and size at diagnosis, the introduction of treatment with GHr and the final size.

Results
The mean age at diagnosis was 8.9±0.4 years, 45% over 10 years. The size at diagnosis was –4 DS/M and –3DS/TC. The age at initiation of treatment was 10±0.1 years with a mean treatment duration of 5±0.1 years. Ten patients were not able to be processed. Final height was –3, 5 DS/M and –2.5 cm/TC with an average of 144±0.2 cm for patients treated and –4DS/M and –4 DS/TC for the others.

Discussion and conclusion
Unfavourable results in our patients are explained by delayed diagnosis. Treatment may not be efficace if the GHr treatment is not given precociously patient inflammators background processes, and infiltrating tumour of the pituitary stalk are rare. They are a heterogeneous group of lesions responsible of partial hypopituitarism or global objective. Search for of thickening of the pituitary stalk aetiologies and specify the clinical aspects.

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EP113
Sarcopenia, more that dehydration, may be associate to underweight Portuguese centenarians
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Introduction
Fat-free mass has a functional significance in aging. The objective of this study was to evaluate the prevalence of underweight in a Portuguese population of centenarians and their relationship with dehydration or sarcopenia.

Methods/design
Anthropometric data were obtained using standard procedures from 252 centenarians (100.26±1.99 years), 77.8% women (W). Body composition was assessed by tetrapolar bioimpedance. It was considered dehydration: total body water (TBW) (%) <45 (W) and <50 male (M), and excess of fat mass (FM) (%): >35 (W) and >25 (M). The fat mass index (FMIndex); (FM/kg/height²) and muscle mass index (MMIndex); (MM/kg/height²) were calculated. Statistical methods: T-student, ANOVA, χ², linear correlation.

Results
In the sample, 61.4% had normal weight (BMI = 21.42±1.86), but 25.3% were underweight (BMI = 16.84±1.51), and of these, 28.8% were women. Instead, overweight (BMI = 27.52±2.40) checked in 13.3% in both genders, which was predominating in men (10.6 vs 22.6%). Dehydration was observed in 12.9% of subjects and was tendentiously higher in women (15.4 vs 5.0%, P = 0.03). Excess of FM was found in 6.0% of subjects with no gender differences (P = 0.229). In the overweight subgroup there were differences in TBW (P = 0.003) and FM (P = 0.022) between genders, which was not observed in the underweight subgroup. The FMIndex in underweight or overweight subgroups did not vary significantly with gender. Muscle mass and MMIndex were different between genders, with the lowest values observed in underweight W compared to M (51.7±5.96 vs 36.3±5.84; P = 0.01) or to the other subgroups. There was a direct linear correlation between BMI and MM ((M=M)=0.749; [W=W]=0.683) and inverse with TBW ((M=M)=−0.428; [W]=−0.397), men and women, P <0.001.

Conclusion
The underweight was more represented in the Portuguese centenarians. More than body water and FM, sarcopenia may be responsible for this low weight particularly in the women.

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EP114
Salt and puberty: self-regulated salt intake and the effect of salt on puberty
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The onset of puberty is changing in western countries. Puberty is the activation of the reproductive system, and is initiated by a complex series of events that are not fully understood. BMI has been linked to the advancement of puberty, but is unlikely to be the whole story as girls with a normal BMI are also advancing through puberty earlier. It is well known that western diets are high in calories, but the high salt content in these diets has been overlooked as a potential contributing factor. Salt consumption in the US and Europe far exceeds the recommended daily values. We hypothesize that salt intake may affect the timing of puberty. Our study on Sprague-Dawley rats fed a high salt diet from weaning (Day 21) have a significant delay in the onset of puberty compared to a control, 0.3% salt, diet. Corticosterone levels were not different between control and high salt-fed rats, suggesting that the pubertal delay was not mediated by stress. FPG-21, which has been implicated in puberty onset, also did not differ between high salt and control rats. Salt intake was then varied to determine if lower salt intake may be stimulatory to puberty. Rats were fed no salt (0.01%), control (0.3%), 2%, or 4% salt. Rats fed no salt showed significantly delayed puberty. Our data showed a trend for salt to cause a slight advancement in puberty, whereas 4% salt was not significantly different from control. To establish optimal salt-intake, rats were given the option of drinking saline (0.5% salt) or pure water while being fed no salt, 0.3%, or 2% salt in their chow. Rats fed no salt consumed 3.6 ± 0.8 mg/g per day salt compared to total food intake. Control rats consumed 2.9 ± 0.9 mg/g per day salt, and 2% rats fed salt consumed 5.1 ± 0.5 mg/g rat per day total salt. This data suggests that our 2 and 4% high salt diets are within the physiologic range of salt consumption in rats. Our data shows that high salt can delay puberty at the highest levels, but may advance puberty at lower levels. Current salt loading in western populations has the potential to effect reproductive health, and warrants further attention.

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EP116
Biochemical and molecular modelling analyses explain the functional loss of HSD17B3 in 17β-Hydroxysteroid dehydrogenase type 3 (encoded by HSD17B3) catalyses the conversion of Δ4-androstene-3.17-dione to testosterone and has a key role in male sexual development. Mutations in the HSD17B3 gene can result in reduced enzyme activity and decreased testosterone synthesis, leading to a rare autosomal recessive aetiology of 46, XY Disorders of Sex Development (46, XY DSD) named 17β-HSD3 deficiency. Here, we characterised three Tunisian patients from non-consanguineous families with a 46, XY karyotype and impaired virilisation of the external genitalia. The hormonal analysis and family history pointed to 17β-HSD3 deficiency. Genetic analysis revealed novel compound heterozygous mutations, i.e. a missense mutation (G133R) and a premature stop codon (C206X) in the HSD17B3 gene. Using site-directed mutagenesis, an expression plasmid for 17β-HSD3 G133R was constructed. Additionally, expression plasmids for substitutions of glycine 133 to alanine (G133A), to phenylalanine (G133F), and to glutamine (G133Q) were created. WT and mutant enzymes were expressed in HEK-293 cells, followed by assessment of the conversion of radiolabelled Δ4-androstene-3,17-dione to testosterone. Mutants G133R, G133Q and G133F were almost completely inactive, whereas G133A retained more than 80% of WT activity. A homology model of 17β-HSD3 predicted that the loss of activity is due to a disruption of the cofactor-binding site. While an alanine at position 133 was still tolerated, more bulky side-chains led to steric hindrance thus preventing cofactor binding. The glycine at position 133 is highly conserved among the short-chain dehydrogenases. The functional analysis and homology modelling revealed an important role of this residue in the structural arrangement of the cofactor binding pocket. The results provide an improved mechanistic understanding of the 17β-HSD3 structure-function relationship and explained the 17β-HSD3 deficiency observed in the patients.

Disclosure
Swiss National Science Foundation 31003A_140961.

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EP117
Search for DHEASism and DHEASoma

Recently we described clinical case of 38-year-old fertile woman with sudden onset of a multiple clinical symptoms: weight gain, secondary amenorrhea, hirsutism and seizures. Adrenal tumour co-secreted high amounts of DHEA sulfate, testosterone (T) and aldosterone (A) (Matulevicius et al. 2014). The symptoms of the disease disappeared after laparoscopic removal of adrenal tumour, which proved to be an adrenocortical oncoyctoma. A hypersecretion of A remained after resection of adrenal tumour, suggesting subclinical hyperandrogenism. In attempt to find more such cases, we analysed results of DHEA determinations in two university hospitals of Lithuania (Vilnius and Kaunas) during 1 year – 2014. We checked 1215 DHEA results of 18–50-year-old woman determinations in two university hospitals of Lithuania (Vilnius and Kaunas) during 1 year – 2014. We checked 1215 DHEA results of 18–50-year-old woman to investigate our hypothesis. Increased DHEAS was considered when patient’s DHEAS concentration was higher than maximal value of DHEAS indicated in the assay kit (11.76%) and was found in 143 cases. Mild increase was in 87.4%, moderate increase – in 9.8% and high increased – in 2.8%. These results confirm that mild increase of DHEAS is frequent (DHEASism). High increase of DHEAS is very rare – found only in four patients (DHEASoma). From these DHEASoma is confirmed in one patient and three are under investigation. Analysing the publications of the last 10-years about increased DHEA concentration we found that increased DHEAS concentration is frequent in 18–50-year-old woman. These findings are linked to the polycystic ovary syndrome. In this syndrome DHEAS is increased in 20–30%. Elevated DHEAS was found in 9/11 adrenal cancers. Apart of our case, we found two more DHEASoma benign tumor cases in literature. Rarity of DHEASoma suggests that multicentral and multidisciplinary efforts are necessary for discovering and defining the disease.

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EP118
Psychological problems in children with diabetes mellitus type 1
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**EP119**

**Influence of food on daily profiles of steroids**

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Introduction

Whereas the daily profiles of the main steroid hormones are well known, minor differences in the course of their levels related to defined and standardised food intake were studied rarely. The experience of DM 1 was 4.9 ± 3.6 years, HbA1c levels – 8.9 ± 1.5 mmol/l, insulin – 1.67 ± 0.3 IU/kg. ANOVA DSRS showed that sleep deprivation was dependent on the experience of DM 1 (P = 0.036) and glucose level (P = 0.045). Low concentration (P = 0.003), mood (P = 0.001), higher irritability (P = 0.017), low emotional (P = 0.01), low confidence (P = 0.044) levels, pessimism (P = 0.027) levels were dependent on the stage of Tanner. At the same time low mood was dependent on the glucose (P = 0.05) and insulin (IU/kg) (P = 0.018) levels; higher irritability – with the experience of DM 1 (P = 0.04); low confidence with insulin (IU/kg) (P = 0.045); weight increasing – with insulin (IU/kg) (P = 0.036). CBCL and QL showed that disorganization (P = 0.02), the loss of time due to DM 1 (P = 0.003) and time, conducted on glucose monitoring (P = 0.005) were correlated with the experience of DM 1. The higher experience of DM 1 the more children are afraid of teacher’s attitude (P = 0.009).

Conclusions

We found, that some psychological problems in children with DM 1 (sleep deprivation, low mood, low confidence) were dependent on the compensation of DM 1 and were increased due to puberty and the experience of DM 1.

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**EP120**

**Six-month interim safety and efficacy of different dose levels of transCon hGH administered once weekly versus standard daily human growth hormone replacement therapy in pre-pubertal children with growth hormone deficiency (GHD)**

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Background

TransCon hGH is a long-acting prodrug of recombinant human GH (hGH) that releases into the blood compartment fully active unmodified hGH. TransCon hGH was shown in two Phase 1 studies and a Phase 2 study in AGHD to be safe and well tolerated and inducing an IGF-I pharmacodynamic response within the normal range throughout the dosing period. This interim analysis consists of 25 patients completing all 6 months of treatment.

Objectives

The objective of this study is to investigate i) safety and tolerability, ii) pharmacokinetics and pharmacodynamics, and iii) efficacy of TransCon hGH in children with GHD.

Design and methods

Pre-pubertal, treatment naïve GHD children received s.c. injections of one of three once-weekly TransCon hGH doses (0.14, 0.21 or 0.30 mg hGH/kg per week) or daily hGH (Genotropin; 0.03 mg hGH/kg per day = 0.21 mg/kg per week) over a 6-month treatment period.

Results

Mean annualised height velocities ranged from 11.9 cm for the 0.14 mg/kg per week dose to 14.5 cm for the 0.30 mg/kg per week dose, which were comparable to 11.5 cm for the active comparator, Genotropin at a 0.21 mg/kg per week dose. No SAEs occurred and injection site reactions were generally mild and transient and occurred in only a few patients. Maximum hGH blood concentrations are comparable between equivalent weekly doses of TransCon hGH and daily hGH; and a dose–proportional increase in IGF-I levels into the normal range was observed for the three TransCon hGH dose levels.

Conclusions

To date, TransCon hGH has demonstrated efficacy and safety comparable to that observed with daily hGH. Injection site reactions have been mild and similar to what is expected with daily hGH injections, with no nodule formation or lipatrophy noted. This TransCon hGH Phase 2 study conducted in a paediatric population confirms the excellent safety and efficacy profile observed in previous clinical trials.

Disclosure

This study was sponsored by Ascendis Pharma A/S.

DOI: 10.1530/endoabs.37.EP120
Results
Patients from the investigational groups I, II, and III presented with significantly higher concentrations of androgens: DHEAS ($P < 0.000$), testosterone ($P < 0.000$), androstenedione ($P = 0.007$), and BAT ($P < 0.000$) than the controls. Moreover, we found significant inverse correlations between the concentrations of testosterone and androstenedione ($r = -0.420, P < 0.000$), SHBG and DHEAS ($r = -0.391, P < 0.000$), SHBG and androstenedione ($r = -0.272, P < 0.000$) in group II and III participants.

Conclusions
Determination of the hormonal profile of girls with acne is vital for the management of this condition and prevention of its recurrence. Juvenile acne is a clinical marker of hyperandrogenism and can be considered a transient manifestation of puberty in teenage girls.

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**EP122**

The NCEP ATP III criteria may overestimate the diagnosis of metabolic syndrome in obese and overweight adolescents

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Introduction
The diagnosis of the metabolic syndrome is less definite in children and adolescents compared to adults. The International Diabetes Federation (IDF) and National Cholesterol Education Program Adult Treatment III guidelines (NCEP ATP III) have proposed two different criteria for its diagnosis in these age groups. In this study we planned to compare these two criteria in detecting the metabolic syndrome in obese and overweight adolescents in a study group in Northern Cyprus.

Subjects and methods
A total of 274 obese and 46 overweight adolescents were included from the northern region of Cyprus. The mean age was 13.72 ± 1.15 years (11.2–17). 156 (48.8%) were girls and 164 were boys (51.2%). We measured the subjects' blood pressure, fasting blood glucose levels, HDL-C levels, triglycerides, body weight to the nearest 0.1 kg, body height to the nearest 0.1 cm. We calculated the BMI by dividing the weight in kilograms to the height in centimetres squared.

Results
Metabolic syndrome was detected in 18.2 and 47.8% in obese adolescents and 17.4 and 30.4% in overweight adolescents according to the IDF and NCEP ATP III criteria respectively.

Conclusions
The prevalence of metabolic syndrome was much higher when using the NCEP-III criteria compared to the IDF criteria both in obese and in overweight adolescents leading to a debate in determining which criteria to be used.

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**EP123**

Is there a link between lipid profile and thyroid function modification during somatropinum treatment for GH deficiency in children? 

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Background
Previous studies suggested that treatment with somatropinum in children with GH deficiency (GHD) may alter lipid profile and pituitary-thyroid axis function. However, results are divergent and data regarding a possible association between changes of thyroid function and of circulating lipids are scarce. The aim of this study was to report the changes of the lipid profile in children with GHD treated with somatropinum and the relationship between thyroid function and circulating lipids modifications.

Patients and methods
We performed a retrospective study in which we included children diagnosed with GHD ($n = 101$, 68 males and 33 females with a mean age of 8.6 years) treated with somatropinum during January 2008–January 2012. We recorded from the medical files the following data: weight, height, total-, HDL-, LDL-cholesterol, triglycerides, TSH, and free T4 at inclusion (start of the treatment) and every 6 months during the first year of treatment with somatropinum.

Results
Patients with GHD had increased serum triglycerides levels at 6 months after initiation of treatment (from a mean of 60.41 mg/dl at inclusion to 79.93 mg/dl, $P = 0.025$), increased HDL (from a mean 55.35 mg/dl at inclusion to 65.50 mg/dl, $P = 0.05$) and decreased LDL after 1 year (from a mean of 99.35 to 88.35 mg/dl, $P = 0.05$) Although, TSH and free T4 decreased at 6 and 12 months in comparison with baseline, this modification was not statistically significant. However, the changes of HDL and LDL level, were significantly correlated with the TSH levels modification from baseline ($r = 0.549$, $P = 0.015$ for triglycerides and $r = 0.731$, $P = 0.011$ for LDL).

Conclusion
Our study showed that lipid profile significantly changes during treatment with somatropinum for GHD in children and this alteration could be partially due to a slight modification of thyroid function. However, further prospective studies are necessary to clarify this aspect.

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**EP124**

Haploinsufficiency of the SHOX gene associated with mosaicism 45,X/46,XY with chromosome Y ring as causes of delayed growth and puberty

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Introduction
The height growth is regulated by multiple factors, including specific genetic mutations that cause correct differentiation and proliferation of chondrocytes. We present a case of double association of haploinsufficiency of the SHOX gene with a mosaic 45,X/46,XY (Y) karyotype responsible for growth and pubertal delay.

Case
Male patient, observed in endocrinology consultation at age of 12, with constitutional delay of growth (below the 5th percentile) and pubertal delay. Hormonal analytical study excluded GH deficit and showed reduction of total testosterone (0.2 ng/ml) and free testosterone (0.2 pg/ml) and proof of GnRH with abnormal response. Coeliac disease was excluded. Radiographic study presented delay of skeletal maturation and echographic study established the presence of well positioned testes with normal morphology. Magnetic resonance of the pituitary was also normal. Karyotype’s study was performed and revealed the presence of a mosaic 45,X/46,XY. About 63% of the cells didn’t had the SRY gene.

He made two cycles of 4 months with testosterone enanthate (dose of 62.5 mg/month) with regular progression of pubertal development, however the patient kept growth delay in the follow up. Now, at the age of 18, he was performed karyotype study with extended banding that confirmed an aneuploid line for the Y chromosome (45,X) without SRY gene, and a line with a ring Y chromosome (46,Xr (Y)) without the SHOX gene and the presence of SRY.

Conclusions
The case described highlights the importance of accurate diagnosis of sex chromosome abnormalities and mutations of the SHOX gene to establish a diagnostic strategy and appropriate therapy in patients with constitutional delay of growth and puberty. We also recommend for the need of regular monitoring, because the potentially associated complications.

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Endocrine and metabolic profiles in adults with Prader–Willi syndrome
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Introduction
Prader–Willi syndrome (PWS) is a genetic syndrome usually diagnosed in childhood. Its reported prevalence ranges from one in 8000 to one in 45 000 with geographical variation. Clinical manifestations include obesity, hyperphagia, short stature, incomplete sexual development, and cognitive disabilities. The majority of published data regarding PWS comes from paediatric populations.

Materials and methods
This is a retrospective observational study of adult patients with PWS performed in an Irish tertiary referral centre. We collected anthropometric measurements, hormonal data, results of genetic testing, and clinical data regarding co-morbid conditions, psychological, and social circumstances.

Results
Twenty-two adult patients (15 women) with a diagnosis of PWS were identified. The median age was 24.5 years. Median height and BMI was 154.3 cm and 41.7 kg/m² respectively. Eighteen of patients were assessed for GH deficiency (GHD), 15 using the insulin tolerance test. Sixteen (88.2% of the patients tested) had severe GHD. Fifteen received GH therapy. Height velocity was 4 cm in the first 6 months and 9 cm in the first year of therapy. Fifty percent of patients had evidence of obstructive sleep apnoea; 90.9% had spinal scoliosis; 81.8% had diabetes; 13% had an abnormal HbA1c. 22/22 had learning disabilities, and 50% had associated psychiatric diagnoses. There was no difference in BMI, height, lipids, fasting glucose between GH treated and untreated patients. However the number of patients was small so this could be underpowered to detect a true difference.

Conclusion
Adult patients with PWS have multiple endocrine abnormalities and require careful follow up and management. Early diagnosis and management of endocrine manifestations will potentially improve health and developmental outcomes in adulthood.

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Diagnostic value of amino-terminal peptide of type I procollagen when retesting GH deficiency in the transition period
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N-terminal peptide of type I procollagen (P1NP) is a marker of GH (hGH) anabolic action on bone formation. We evaluated the diagnostic value of P1NP in GH deficiency (GHD) in the transition period using receiver operating characteristic (ROC) plot analysis. We compared the diagnostic value of P1NP with IGF1. 16 male patients (chronological age, 15.2–17.5) was selected. GH secretion was evaluated in IGHD group using insulin replacement therapy during childhood (ten IGHD and six MPH) were evaluated at minimum 3 months after completion of treatment (1.62 ± 1.46 years from mGH withdrawal). A control group (CG) of nine healthy males (chronological age, 15.2–17.5) was selected. GH secretion was evaluated in IGHD group using insulin tolerance test and were divided as persistent IGHD (three patients) or reversible IGHD (seven patients) according to a GH cut-off below or above 5.6 nmol/L. There were no significant difference between IGF1 and P1NP in the control group and reversible IGHD group. The SDS for IGF1 and P1NP was calculated from the 16 participants with normal GH status (controls and reversible IGHD). The ROC plot showed that the best IGF1 SDS cut-off line was 0.76 (sensitivity (S), 87.5%; specificity (Sp), 88.9%, AUC = 0.944). For P1NP SDS, the best cut-off line was 0.81 (sensitivity (S), 81.3%; specificity (Sp), 66.7%, AUC = 0.743).

Conclusion
IGF1 is a better GH biomarker for diagnostic of persistent growth deficiency in the transition period with better specificity and sensibility comparing to P1NP.

Disclosure
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Precocious puberty in the obese child as a diagnostic challenge
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The aim of this study was to evaluate whether the coexistence of obesity in children with precocious puberty symptoms influences significantly the diagnostic process.

Material and methods
We retrospectively analysed a group of 200 children’s records (F/M 164/36) hospitalised because of precocious puberty suspicion. The analysis evaluated the nutritional status based on BMI percentile level, compatibility between the bone age and the chronological age; and the final clinical diagnosis.

Results
In the analysed group excessive body weight was found in 66 (33%) children – overweight in 34 (17%) and obesity in 32 (16%) patients respectively. It is noticeable that children with excessive body weight are significantly more likely to have mild variants of precocious puberty (71% vs 66.4%) despite the fact that the accelerated bone age in this group was more frequently observed (47% vs 24.6%). In the group with mild variant of PP and accelerated bone age (n = 41 (28.9%)) up to 75.6% of children were overweight or obese. In the group of CPP accelerated BA was observed only in 23 (52.3%) children. Frequently recognized variant of PP in obese children was premature pubarche (n = 20 (62.5%)).

Conclusions
Obesity and overweight significantly modifies puberty, and by accelerating the bone age can hinder the initial diagnosis of PP. The bone age acceleration seems to be poor indicator of central precocious puberty, especially in obese children. The population of overweight and obese children is dominated by a mild variant of precocious puberty – premature pubarche.

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Is thyroid function related to masked hypertension?
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Background
Thyroid hormones affect almost all the tissues of the body and their cardiovascular effects are very significant. The relationship between masked hypertension (MHT) and thyroid hormones is not known. Therefore, we sought to investigate any relationship between patients with MHT, newly diagnosed by home blood pressure monitoring, and thyroid hormones.

Methods
Patients older than 18 years of age without a previous diagnosis of hypertension and presenting to the Outpatient Department with hypertensive symptoms were enrolled. Patients were categorized into three groups as MHT, primary hypertension (PHT) and normotensive, according to blood pressures taken at home and office. The levels of TSH, free triiodothyronine (T3), and free thyroxine (T4) were measured by electro-chemiluminescence immunoassay in the three groups.

Results
Of the 712 participants enrolled in the study, 206 had PHT, 73 had MHT, and 433 were normotensive. The average log(TSH) level was higher while average T4 level was lower in the PHT group as compared to the MHT and normotensive groups. Log(TSH) and T4 levels were similar in the MHT and normotensive groups. Stepwise multiple regression analysis showed average systolic and diastolic blood pressures to be related to log(TSH), T3 and presence of hyperthyroidism in the PHT group. No such relationship was found in the MHT and normotensive groups.

Conclusion
In conclusion, no relationship was found with thyroid hormones in patients with MHT in contrast to patients with PHT. Randomised controlled studies with a larger population size and longer follow-up duration are needed to understand the relationship between blood pressure values and thyroid hormones in patients with MHT.

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Effect of metformin on sex steroid levels in postmenopausal type 2 diabetic patients

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Introduction
Metformin treatment was associated with decreased risk of various cancers including breast cancer. Exposure to sex steroid is related with increased risk of breast cancer. In this study, we aimed to evaluate the effect of metformin treatment on serum levels of sex steroids and sex hormone binding globulin (SHBG) in postmenopausal women with type 2 diabetes mellitus.

Methods
Postmenopausal patients with newly diagnosed type 2 diabetes were recruited to the study. Before starting life-style modifications and metformin treatment anthropometric measurements were done and fasting blood samples were collected in order to evaluate insulin, glucose, HbA1c, serum levels of sex hormones, and SHBG. All of the basal tests were repeated for each subject at the end of 12 weeks.

Results
At the end of 12 weeks, 36 patients completed the study and were included into analyses. Five of 36 patients did not use metformin due to gastrointestinal side effects or noncompliance with therapy. Remaining patients used at least 500 mg to maximum 2000 mg/day of metformin treatment. Mean body-weight and body fat mass, fasting insulin, HbA1c levels significantly decreased in patients who used metformin. Patients receiving metformin treatment also showed significant decrease in testosterone (−28%), oestradiol (−9%), and oestrone levels (−11.5%), and significant increase in DHEAS (8.9%) and SHBG (4.5%) levels. A borderline significant decrease was seen in androstenedione levels as well. Fasting plasma glucose and oestrone sulphate levels did not change significantly. When compared to the patients who did not use metformin therapy, changes in oestradiol levels were significant, and changes in estrone and testosterone levels marginally significant in patients receiving metformin.

Conclusion
Metformin treatment may have favourable effect on breast cancer risk through decreasing androgen and oestrogen levels in postmenopausal type 2 diabetic patients.

Serafrom prolactin levels in transgender persons before and during cross-sex hormonal treatment

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Introduction
Gender dysphoria refers to the incongruence between the subject’s experienced sex on the one hand and the assigned sex on the other hand. Several studies assume a relationship between oestrogen substitution therapy and serum prolactin levels.

Aim
The aim of this study is to get more insight into the effect and time-course of changes in serum prolactin levels during cross-sex hormone therapy.

Methods
This prospective study included 82 transgender persons who completed 1 year of cross-sex hormonal treatment. The aim of this study was to get more insight into the effect and time-course of changes in serum prolactin levels during cross-sex hormone therapy.

Results
At the end of 12 months, 36 patients completed the study and were included into analyses. Five of 36 patients did not use metformin due to gastrointestinal side effects or noncompliance with therapy. Remaining patients used at least 500 mg to maximum 2000 mg/day of metformin treatment. Mean body-weight and body fat mass, fasting insulin, HbA1c levels significantly decreased in patients who used metformin. Patients receiving metformin treatment also showed significant decrease in testosterone (−28%), oestradiol (−9%), and oestrone levels (−11.5%), and significant increase in DHEAS (8.9%) and SHBG (4.5%) levels. A borderline significant decrease was seen in androstenedione levels as well. Fasting plasma glucose and oestrone sulphate levels did not change significantly. When compared to the patients who did not use metformin therapy, changes in oestradiol levels were significant, and changes in estrone and testosterone levels marginally significant in patients receiving metformin.

Conclusion
Metformin treatment may have favourable effect on breast cancer risk through decreasing androgen and oestrogen levels in postmenopausal type 2 diabetic patients.

How much insulin resistance in polycystic ovary syndrome: comparison of HOMA and insulin resistance (Belfiore) index models

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Background
Polycystic ovary syndrome (PCOS), the commonest endocrinopathy of women in the reproductive age is often accompanied by insulin resistance (IR). The aim of the study was to assess the prevalence of IR in women diagnosed with PCOS, where IR was assessed by methods most commonly used in clinical practice, i.e. homeostatic model assessment (HOMA) and insulin resistance index (IRI), also known as the Belfiore index.

Patients and methods
The study involved 137 women diagnosed with PCOS according to the Rotterdam (2003) criteria, age (mean ± s.d.) 25 ± 7 years, BMI 27.61 ± 7.43 kg/m2. IR was assessed according to the HOMA method (glucose (mmol/l) × insulin (μU/ml)/22.5) and IRI methods, where IRI, can be obtained through the formula: 2/((1/(INSp × GLYp)) + 1), where where INSp, GLYP = insulinemic and glyceric, areas during 75 g OGTT. IR was diagnosed for IRI > 1.25.

Results
There was a strongly significant (P < 0.0001), but still relatively moderate correlation between IRI and HOMA methods (r = 0.5 and r = 0.57 for a linear and non-linear model respectively). IR was much more prevalent according to IRI (49.6%) than according to HOMA (22.6 and 15.8% for 3.46 and 3.8 cut-off points,
respectively, P<0.01). The majority of patients with high HOMA also had high IRI (e.g. 86% for HOMA >3.8), but the majority of patients with raised IRI, would not be diagnosed as insulin resistant according to HOMA (61.7 and 73.5%, for HOMA$_{4.6}$ and HOMA$_{5.0}$ respectively). IRI concentrations were higher among patients with concomitantly raised HOMA (1.55±0.18 vs 1.44±0.14, P=0.014 and 1.60±0.18 vs 1.44±0.13, P=0.0008 for HOMA$_{4.6}$ and HOMA$_{5.0}$ respectively).

Conclusions
IRI, based on glucose and insulin measurements during OGTT demonstrates more cases of insulin resistance than HOMA model in women with PCOS. Therefore, detection of insulin resistance among women with PCOS is highly method-dependent with more severe cases being detected with HOMA than with IRI.

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**EP133**

**Surrogate markers of insulin resistance obtained from oral glucose tolerance test in different phenotypes of polycystic ovary syndrome**

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**Introduction**
Insulin resistance (IR) is a well recognised feature in women with polycystic ovary syndrome (PCOS). The aim of this study was to analyse IR indices obtained from oral glucose tolerance test (OGTT), in different PCOS phenotypes.

**Methods**
We evaluated 240 PCOS women (PCOS: 24.86±5.8 kg/m$^2$; controls: 26.14±4.2 kg/m$^2$) with the OGTT protocol during 60 minutes and the results were compared with those obtained in healthy volunteers (controls: 25.25±4.98 years) diagnosed using ESHRE/ASRM criteria and 70 BMI-matched healthy women (controls: 26.14±4.86 kg/m$^2$; 30.76±5.82 years). PCOS group was divided into four phenotypes: A (anovulation (ANOV), hyperandrogenism (HA), and polycystic ovary morphology (PCOM)), B (ANOV and HA), C (HA and PCOM), and D (ANOV and PCOM). Phenotype D had lower BMI in comparison to all other phenotypes (P<0.05). Standard OGTT with 75 g glucose was performed in all subjects. IR was estimated by the homeostasis model assessment of IR (HOMA-IR), insulin sensitivity index (ISI), hepatic IR index (HRI), and insulinogenic index (IGI). The areas under insulin (AUCi) and glucose (AUCg) and their ratio, termed the insulin secretion-sensitivity index-2 (ISSI-2) were calculated.

**Results**
The whole PCOS group in comparison with controls had higher levels of basal glucose (4.89±0.45 mmol/l vs 4.57±0.50 mmol/l, P=0.003) and insulin (1.07±1.03 mmol/l vs 1.19±0.53 mmol/l, P<0.001). HOMA-IR (3.64±2.38 vs 2.66±1.48, P<0.001), HRIIR (3.98±2.65 vs 2.20±0.85×10$^{-3}$, P=0.027), GS (22.15±15.86 vs 10.31±4.13, P=0.027), AUCi (711.63±153.87 vs 670.68±86.48, P=0.012), AUCg (7847.97±4660.48 vs 4647.80±1665.78, P=0.029), and ISSI-2 (1.08±0.54 vs 0.72±0.02, P=0.019) and while ISI (4.50±2.14 vs 6.40±2.71, P=0.032) was lower. Phenotype D had higher levels of basal insulin and HOMA-IR then phenotypes A, C, and D while AUCi, HRI, ISSI-2 were higher and ISI was lower then in phenotypes C and D. There were no differences in basal glucose, AUCi and ISI between phenotypes.

**Conclusion**
In our group of women with PCOS, classical hyperandrogenic phenotype B was characterised with the most exaggerated indices of IR.

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**EP134**

**A case of dyskeratosis congenita associated with hypothyroidism and hypogonadism**

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**Introduction**
Dyskeratosis congenita is a rare multisystemic disease characterised with atrophy on skin, pigmentaion, nail dystrophy, leukoplakia in mucous membrane, bone marrow failure, and tendency to malignancy. We present a rare case of dyskeratosis congenita associated with hypothyroidism and hypogonadism.

**Case**
A 30-year-old male patient was referred to Endocrinology Department with the findings of microtrophism and atrophic testicles. His parents had cousin marriage.

Physical examination results: BP: 130/80 mmHg, height: 172 cm, weight: 83 kg, and BMI: 28 kg/m$^2$. There were hypopigmented skin lesions in the whole body. The skin was dry and the nails were dystrophic. His axillary and pubic hair was normal but facial hair was scarce. He had alopecia in 1/3 of outer eyebrow (Ommunus sign) and saddle nose. Microopenis and testicles were found to be atrophic. The laboratory findings: Hb: 12.5 g/dl, plt: 187 000/mm$^3$, ferritin: 1.4 pg/ml, total testosterone: 0.70 ng/ml, FSH: 77.28 mIU/l, LH: 15.38 mIU/l, E$_2$: <20 pg/ml, prolactin: 6.77 ng/ml, DHEAS: 222.1 µg/dl, free T$_3$: 3.35 pg/ml, free T$_4$: 0.98 ng/dl, TSH: 10.88 mIU/l, anti-TG: 203 IU/ml, ACTH: 24.1 pg/ml, and cortisol: 13.34 µg/dl. Hypogonadotropic hypogonadism was suspected as testosterone was low and FSH and LH were high. Hyperkeratotic keratoderma was found in skin biopsy. In the biopsy of lymph node from right cervical, we found disseminated histiocytic proliferation that changes the normal appearance of lymph node and granulomas that are characterised with rare giant cell formation and that don’t include necrosis.

**Conclusion**
Dyskeratosis congenita is a rare disease showing X-linked recessive inheritance along with autosomal dominant and recessive forms. Although the pathogenesis of the disease is still unknown, DAX1 gene localised to Xq28 is thought to be responsible for the X-linked dyskeratosis congenita. Our patient is still genetically studied. In this syndrome, the association of hypothyroidism and hypogonadism should be kept in mind.

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**EP136**

**The impact of bleeding patterns and hormonal contraceptives on migraine headache: a retrospective cross-sectional study**

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**Introduction**
Clinical studies revealed an increased incidence of migraine attacks in conditions with falling levels of plasma oestrogen in the perimenstrual phase of the menstrual cycle and during the hormone-free interval in women taking combined oral contraceptives.

**Objective**
The purpose of the study was to assess the connection between menstrual cycle, bleeding patterns of women with migraine and the clinical characteristics of the migraine attacks.

**Methods**
The questionnaire-based survey (n=186) was undertaken in the South-Eastern Hungary with the collaboration of the Department of Neurology and the Department of Obstetrics and Gynaecology. We invited all women with M0 and MA in the Outpatient Headache Unit of the Department of Neurology, Szeged, Hungary to participate in the questionnaire-based study. We collected a data in two time periods: between 2006–2009 and 2013–2014. We collected the answers via three ways: personal face-to-face interviews, online and postal way. The main outcome measures were to describe the menstrual pattern of women with migraine, the relationships between menstrual cycle and clinical characteristics of the migraine attacks.

**Results**
Our study group consisted of 108 (52%) women with M0 and 78 (48%) women with MA. The average age of the patients at the diagnosis of migraine was 18.79±6.97 years. The Pearson’s correlation test revealed a relationship between duration of menstrual cycle and the intensity of headache pain (P=0.012). However, there was no significant relation between the intensity of headache pain and other study parameters (e.g. duration of use of COC, length of bleeding, menstrual cramps, amount of bleeding, and BMI).

**Conclusions**
According to our best knowledge this is the first study in Hungary to describe contraceptive habits of migraineurs and the connection between the duration of menstrual cycle and intensity of the migraine head pain.

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**EP137**

**Constitutive and inducible regulation of PEPCK isoform genes in human cells**

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**Introduction**
Phosphoenolpyruvate carboxykinase (PEPCK) is the key rate determining enzyme of gluconeogenesis pathway. PEPCK exists in cytosolic (PEPCK-C) and mitochondrial (PEPCK-M) isoforms. PEPCK isoforms maintain glucose/fatty acid homeostasis and is being explored as a therapeutic target for treating metabolic diseases. We tested the influence of a naturally occurring compound Genistein (a soy derived isoflavone) to constitutively regulate PEPCK isoforms to address its potential use as a therapeutic molecule.

**Methods**
HepG2 and fibroblasts were tested for the effects of genistein by western blot; RNA stability was examined by RT-PCR using actinomycin treated cells; transcriptional regulation was performed by reporter assays and CpG DNA methylation was analysed by bisulfite sequencing.

**Results**
Expression and activity of PEPCK isoforms in fibroblasts was lower than in HepG2 hepatoma cells. In HepG2 cells, genistein induced degradation of PEPCK-C transcript and proteins but increased PEPCK-M expression. In fibroblasts, genistein increased PEPCK-C expression through promoter demethylation but PEPCK-M was unaffected. Reporter gene and RT-PCR assays suggested genistein mediated RNA degradation of PEPCK-C in HepG2 cells is due to the existence of AU-rich elements (AREs) in 3′-UTR of the gene.

**Conclusion**
We show an evidence for the regulation of PEPCK-C gene by promoter DNA methylation in human fibroblasts, which might be responsible for maintaining baseline PEPCK activity in non-glucogenic tissues. We show selective effect of soy isoflavone genistein on PEPCK isoform genes in hepatic and extra hepatic cell types by increasing the expression of PEPCK-M as a compensatory mechanism and there by maintaining glucose homeostasis in cells as a pro-survival effect.

Disclosure
Department of Biotechnology, Government of India.

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**EP138**

**Study on the correlation between serum androgens and sexual function in post-menopausal women**

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**Introduction**
Sexual dysfunction could be under the influence of menopause and the changes it causes in hormone levels. The purpose of this study is to examine the correlation between serum levels of androgens and sexual function in post-menopausal women.

**Methods**
This is a community-based, descriptive-analytical study involving 405 post-menopausal women, aged 40–65 years, who had reached menopause up to 3 years prior to the study. A multi-stage, randomized sampling was conducted in the cities of Chalous and Nowshahr. The data was collected using the female sexual function index (FSFI) questionnaire, a researcher-made questionnaire, and blood sampling to study the serum levels of androgens (testosterone and DHEAS), sex hormone-binding globulin (SHBG), and oestradiol in the laboratory. The acquired data was analysed statistically using SPSS.

**Results**
61% of the subjects were suffering from female sexual dysfunction (FSD). Total testosterone levels had a negative correlation with scores in the domain of desire (r = −0.108, P = 0.029), DHEAS levels were positively correlated with scores in the domain of pain (r = 0.113, P = 0.022), and the free estradiol index (FEI) was positively correlated with scores in the domain of pain (r = 0.115, P = 0.020). Satisfaction with marital relationship had a significant positive correlation with total testosterone levels (r = 0.131, P = 0.008) and the free androgen index (FAI) (r = 0.100, P = 0.044). In examining the correlation between FSFI scores and hormone levels, multiple regression analysis showed that serum levels of total testosterone and free androgen index were predicting factors in, respectively, the domain of lubrication (P = 0.042) and satisfaction (P = 0.021).

**Conclusion**
Androgenic hormones can affect certain aspects of sexual function in post-menopausal women. This subject area, however, requires further investigation.

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**EP139**

**Increased circulating urocortin-3 levels is associated with polycystic ovary syndrome**

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**Purpose**

This study aims to compare serum urocortin-3 levels in women with PCOS and healthy women, and establish what role urocortin-3 levels play in PCOS.

**Methods**

Fifty-two patients with PCOS and 55 healthy women were included in the study, matched for age and BMI. Fasting blood glucose (FBG), insulin, hs-CRP, urocortin-3, and free testosterone levels of all participants were measured. HOMA-IR was used to calculate the insulin resistance.

**Results**

Circulating urocortin-3 levels were significantly increased in women with PCOS than in control subjects (54.49 ± 5.77 pmol/l vs 51.28 ± 5.86 pmol/l, P = 0.005). Urocortin-3 levels positively correlated with hs-CRP in PCOS group (r = 0.391, P = 0.004). There was no any correlation between urocortin-3 and other parameters. Multivariable binary logistic regression analysis showed that elevated urocortin-3 levels were associated with PCOS. Receiver operating characteristic curve analysis showed that urocortin-3 levels were useful as a diagnostic marker for PCOS. The optimal cut-off value of urocortin-3 for detecting PCOS was ≥ 51.46 pmol/l, at which the sensitivity was 75% and specificity was 68%.

**Conclusions**

Circulating concentration of urocortin-3 are significantly increased in women with PCOS. Furthermore, increased urocortin-3 levels were associated with PCOS after adjustment for potential confounders. This link in between urocortin-3 and PCOS may be due to an underlying chronic inflammation in subjects with PCOS.

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**EP140**

**Implication of non polar phytocomponents of aloe vera gel in management of polycystic ovarian syndrome**

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**Background**

Aloe vera gel has been proven to have hypoglycaemic, hypolipidemic, and steroid enzyme regulating properties. These are of clinical significance in reproductive aged women. The relationship between IH and metabolic abnormalities are not fully understood. The aim of this study was to evaluate the relationship between IH and metabolic abnormalities.

**Methods**

A total number of 100 idiopathic hirsute women (range 15–45 years) recruitment from a population based cohort study of Tehran Lipid and Glucose Study. Control age-matched women were selected from the same population. Biochemical characteristics of the participants including waist and hip circumferences and ratio, blood pressure, glucose, androgens and lipid profiles, and insulin resistance by HOMA-IR were compared. Differences between the two groups in univariate analysis were detected by independent Student’s t-test for continuous variables with normal distribution or by the Mann-Whitney U test for those without normal distribution. Analysis of covariance (ANCOVA) was used for comparison of groups with adjustment for BMI.

**Results**

The IH subjects had higher BMI and waist to hip circumferences ratio compared with healthy controls, 25.4 (3.2) and 0.83 (0.04) in IH vs 23.9 (4.2) and 0.81 (0.05) in controls (P = 0.02 and P = 0.04) respectively. The mean fasting insulin, HOMA-IR, and TG in IH women were statistically higher than in controls but there were not any statistical differences between them and other biochemical, anthropometric, lipid, and blood pressure profiles after adjustment for age and BMI.

**Conclusions**

Our data suggest that IH did not associate with metabolic disturbances. It seems that no more additional intervention and evaluation are needed in IH subject later in life.

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**EP141**

**Abstract withdrawn.**

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**EP142**

**Is idiopathic hirsutism associated with an increase in metabolic disturbances?**

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**Introduction**

Idiopathic hirsutism (IH) is one of the most frequent complaints affecting 13% of reproductive aged women. The relationship between IH and metabolic abnormalities are not fully understood. The aim of this study was to evaluate the relationship between IH and metabolic abnormalities.

**Methods**

Is idiopathic hirsutism associated with an increase in metabolic disturbances? The IH subjects had higher BMI and waist to hip circumferences ratio compared with healthy controls, 25.4 (3.2) and 0.83 (0.04) in IH vs 23.9 (4.2) and 0.81 (0.05) in controls (P = 0.02 and P = 0.04) respectively. The mean fasting insulin, HOMA-IR, and TG in IH women were statistically higher than in controls but there were not any statistical differences between them and other biochemical, anthropometric, lipid, and blood pressure profiles after adjustment for age and BMI.

**Conclusions**

Our data suggest that IH did not associate with metabolic disturbances. It seems that no more additional intervention and evaluation are needed in IH subject later in life.

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EP143
Prevalence and pattern of menstrual disorders and related factors among Iranian women in reproductive ages: a population based study
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Introduction
Menstrual disturbances can be considered as a sign of reproductive system disorders in women in reproductive ages. These disturbances can be indicators of serious underlying problems. The aim of this study was to determine the prevalence and pattern of menstrual related manifestation among Iranian women.

Methods
This was a population-based study conducted among women (n = 941) aged 18–45 years. The participants who met the eligibility criteria were selected from four provinces using quota stratified cluster sampling, and invited for further comprehensive interview.

Results
The most common menstrual disorders in Iranian women were dysmenorrhea (67.5%) and premenstrual syndrome (54.9%) respectively. Prevalence of other non-anatomical abnormal uterine bleeding was 19.9%. Some demographic factors such as younger age, married at older ages, as well as celibacy was correlated with the incidence of dysmenorrheal (P < 0.5). The results have shown that more than 83% of women younger than 25 years old suffer from dysmenorrheal. Younger women (< 25 years) are 2.3 times as likely to have dysmenorrheal than women 25 years and older (OR =2.3, 95% CI: 1.5–3.7, P <0.0001). Also, never married women are 2.1 times as likely to have dysmenorrhea than married women (OR =2.1, 95% CI: 1.2–3.6, P <0.0001).

Higher BMI and higher levels of education had a significant relationship with oligomenorrhea and premenstrual syndrome respectively (P < 0.5). The result of this study has shown that younger menarche age was significantly associated with the occurrence of menstruation.

Conclusion
Almost one out of every four Iranian women in reproductive age suffers from at least one menstrual disorder. Encouraging women to change lifestyles in reproductive ages, counselling and giving adequate information on menstrual disorders can play a main role in reducing the adverse effects of these disorders.

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EP144
Testosterone level in men correlates with BMI and cardiorespiratory fitness but is not related to age
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Background
Presently it is unknown how much of testosterone decline associated with aging is actually due to ageing per se, and how much is related to weight gain, decreased activity, and other age-related factors. Understanding the modifiable factors associated with low testosterone, such as obesity or cardiorespiratory fitness (fitness) is critical.

Methods
The observational, cross-sectional study included 1653 men, ≥ 50 and <80 years of age, seen between January 2012 and December 2012 for a preventive medical examination and underwent BMI, total testosterone, and objective fitness measurements as defined by the total duration of time on a maximum Balke treadmill test. Treadmill time was then used to estimate metabolic equivalents (METs). All participants underwent morning (0700–0900 h) total testosterone measurement using the standard chemiluminescence method.

Testosterone thresholds were categorized into low (< 250 ng/dl), low normal (250–<400 ng/dl), and normal (≥ 400 ng/dl). We used traditional sample statistics to summarise characteristics of the sample within decades of age and ordered categories of BMI.

Results
While levels of mean testosterone levels in all age groups were in the normal range were statistically different between groups, (50–59 years, testosterone mean = 479.0 ng/dl (S.D. = 175.4); 60–69 years, testosterone mean = 457.2 ng/dl (S.D. = 204.1); and 70–79 years, testosterone mean = 464.6 ng/dl (S.D. = 176.7); trend P value =0.05), although, the trend was statistically different, mean testosterone levels in all groups were in the normal range. The prevalence of low testosterone did not significantly differ between 50–59, 60–69, and 70–79 age groups (< 250 ng/dl) = 7.6–9.3% to 8.7%; trend test P =0.17 but did change with increasing BMI, (< 250 ng/dl) = 3.4–6.8% to 17.8%; trend test P <0.001. Finally, fitness was positively correlated with total testosterone levels (P <0.001) and this correlation persisted after adjustment for age and BMI.

Conclusion
In this group of generally healthy men, there was no decrease in the mean total testosterone level with increasing age, yet we found statistically and clinically negative correlation between testosterone and BMI and positive correlation between testosterone and fitness.

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EP145
Analysing by decade, testosterone undecanoate depot injectable does not increase prostate volume: study during up to 7 years on hypogonadic patients
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Aim
Re-analysing the effect of injectable testosterone undecanoate depot (TUD) in hypogonadic patients.

Materials and method
(A) Patients: at onset 210 men with hypogonadism (median age: 61.5 years). (B) Distribution: by decade; n = 4, 12, 21, 54, 59, 43, 16, and 1. (C) TUD (NebidoR-Bayer-Schering) 1000 mg was injected one per 3 months i.m. (D) Prostate volume (PV) appreciated by per-abdominal ultrasound: 3.5 MHz probe, elliptical volume (cm3), Aloka 550. (E) Time of analysis: before starting testosterone (T0), after 1⁄2 month (T1), 3 months (T2), 6 months (T3), 1 year (T4), 2 years (T5), 3 years (T6), 4 years (T7), 5 years (T8, n = 28), 6 years (T9, n = 12), and 7 years (T10, n = 6). The maximum increment from T0 was noted a M %. Average increment was noted a A %. (G) Statistical analysis: Student’s t-test.

Results
i) All average prostatic volume for decade in figure. Maximum increment (Δ M %) per decade (45.95%: 20; 40.35; 42.5; 45.45; 64.41; and 39.56), including the moment (Δ M % at) and average increment (Δ A %) (Table). (II) PV at T0 increases with age, from minimum 15.38 (19–29 years) to maximum 47.41 (80–89 years), P = 0.0007. (III) Considering all observations (some at 5/6/7 years), TUD did not increase PV significantly (in fact the average of increment in all patients was negative = −12.54%). Δ M % per decade: 20. (IV) Inside a specific decade no significant increase in PV was registered: all P = 0.05; exception: 80–89 decade, P = 0.002, at 3–5 years, (V) In some patients, especially from 50 to 79 years, TUD could decrease slightly prostatic volume.

Conclusions
Considering the risk for prostate (in elderly), testosterone undecanoate 1000 mg depot injectable is a safe treatment, even after 3–7 years of administration. Precautions should be accorded to men over 80 years old, after the 3rd year administration.

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EP146

Testosterone undecanoate 1000 mg at 3 months did not increased prostatic specific antigen level: January 2015
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Aim
To find if testosterone undecanoate (TUD) 1000 mg injection (Nebido®; Bayer-Scherin) at 3 months has a negative effect on prostate.

Materials and method
i) PSA (ng/ml) registered before (T0) and after TUD at T1 (2 weeks) to T10 (7 years) (see Piscoci, this Congress); ii) statistical analysis: t-test, simple correlation, and multiple regression.

Results
(A) Patients at onset: 143 men, 18–96 years, average: 60.38; median: 60. (B) Prostatic volume before TUD (cmc): average: 34.81; in evolution (see Piscoci, this Congress). (C) Average PSA (no patients): before TUD = 1.59 (143); at 1 year = 1.69 (99); 2 years = 1.4 (73); 3 years = 1.85 (48); 4 years = 2 (38); 5 years = 1.86 (26); 6 years = 1.51 (10); 7 years = 2.86 (6). (D) Statistical difference of average: nonsignificant for all the times from 2 weeks to 7 years. (E) Correlation between age and PSA was: i) significant before and after treatment till 2 years but nonsignificant for 3–7 years (PSA did not change as age after treatment). (F) Correlation between PSA and prostatic volume was significant, both before and after treatment (depending on group size); r before TUD = 0.56, at 1 year = 0.51, 2 years = 0.55, 3 years = 0.42, 4 years = 0.5, 5 years = 0.57, 6 years = –0.06, and 7 years = 0.52. (G) Multiple regression test (r² = 0.53–0.99, F = 36.36–4900) shows that PSA level post testosterone does not depend on testosterone but on age, prostatic volume (before and after treatment), and PSA initial level (before testosterone administration); p≤0.001.

Conclusions
i) Testosterone undecanoate 1000 mg injectable i.m. at 3 months did not increase PSA level after 7 years administrations. ii) PSA level post testosterone was in fact dependent only on age, prostatic volume before treatment and PSA level before treatment.

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EP147

Role of elevated serum adiponectin in delayed puberty of thalassemic patients
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Background
Adipose tissue dysfunction can play a role in the neuroendocrine and haematopoietic dysfunctions affecting thalassemic patients. Aim of the work
In this work, we aimed to study the serum levels of adiponectin, an adipocytokine, in Egyptian β-thalassemia patients in relation to their endocrine complications. Subjects and methods
The study included 60 β-thalassemia patients; (major, intermedia, and minor) and 30 healthy age- and sex-matched controls. The diagnosis of thalassemia was based on clinical, haematological, and genetic studies. Anthropometric measurements, clinical neuroendocrinological assessment, iron profile (serum ferritin, serum iron, and total iron binding capacity) and measurement of serum levels of adiponectin using ELISA were performed for all subjects. Our β-thalassemia major and intermedia patients had significantly lower BMI, shorter height, lower weight, delayed growth and puberty while thalassemia minor patients showed no significant delay in puberty compared with healthy controls. Results
A significantly higher level of adiponectin was found in thalassemic patients (median = 3.5 ng/ml) compared to controls (median = 0.4 ng/ml) with the level becoming progressively higher with degree of clinical severity (median = 0.6 ng/ml in minor, 2.5 ng/ml in intermedia, and 4.3 ng/ml in major). The level of adiponectin was negatively correlated to height, weight, and BMI in both thalassemia intermedia and major while it was negatively correlated to puberty only in thalassemia major patients. A clinically significant level of adiponectin was obtained at >0.8 ng/ml for delayed puberty and iron overload (high serum iron and serum ferritin).

Conclusions
We found that high adiponectin levels correlated to iron overload and delayed growth in both β-thalassemia major and intermedia patients as well as to delayed puberty in thalassemia major.

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EP148

Prevalence of autoimmune thyroid markers in euthyroid women with polycystic ovarian syndrome
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Introduction
Polycystic ovarian syndrome (PCOS) is the most common endocrinopathy in women in reproductive age. A condition that causes irregular menstrual periods because monthly ovulation is interrupted and levels of androgens are elevated. It occurs in about 5–10% of women and is considered to be the most common cause of anovulatory infertility in reproductive age.

Objectives
To compare the prevalence, levels of thyroid auto-antibodies in a group of Egyptian women with PCOS and a control group in reproductive age to determine whether women with PCOS have a greater risk of thyroid autoimmune diseases, thyroid dysfunction or not.

Patients and methods
This study was conducted on 45 euthyroid women with PCOS and 18 healthy women as a control in the Outpatient Clinics of Endocrinology, Ain Shams University Hospital. PCOS was defined by the revised 2003 Rotterdam criteria. Thyroid function was evaluated by measurement of TSH and FT₄ levels, anti-thyroid peroxidase, and anti-thyroglobulin antibodies (anti-TPO and anti-TG respectively) as markers for thyroid autoimmunity. All parameters were measured using electrochemiluminescence immunoassay.

Results
Women with PCOS had a significantly higher levels of anti-TPO in comparison to controls (27 ± 10 and 21 ± 10 IU/ml, respectively; P<0.05) with no significant difference in anti-TG, TSH, or FT₄ between the two groups. Patients with PCOS had a non-significant higher prevalence of positive anti-TG and/or anti-TPO in comparison to controls (40 and 22.2%, respectively; P>0.05), anti-TPO alone (28.9 and 16.7%, respectively; P>0.05), and anti-TG alone (22.2 and 11.1%, respectively; P>0.05).

Conclusions
Women with PCOS had a significantly higher levels of anti-TPO than controls that may put them at a higher risk for thyroid autoimmune disease.

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EP149

Stereoselective effects of statins on xenobiotic-metabolising pathways
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Several of currently used drugs are chiral compounds. Majority of them are clinically administered as a racemic (equimolar) mixture of enantiomers. Individual enantiomers of one drug can qualitatively and quantitatively differ in their biological activities (pharmacology, toxicology, pharmacokinetics, etc.). Therefore, enantiopure drugs have been developed and introduced to the therapy. Statins are drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase. Atorvastatin, rosuvastatin, and fluvastatin are the most often prescribed statins. They are marketed as a racemic mixture of these enantiomers; however their enantiopure forms have been introduced to clinic recently (3R,5R-atorvastatin, 3R,5S-rosuvastatin, and 3S,5S-fluvastatin). In this study, we investigated enantioprecise interactions of all four enantiopure forms of atorvastatin, 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 AdR, PXR, and GR were determined using human reporter cell lines. Moreover, we have tested enantiomeric specific effects of statins on the expression of drug-metabolizing enzymes CYPs on mRNA and protein level in primary human hepatocytes.

Disclosure

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EP150

Serum N-terminal pro-B-type brain natriuretic peptide levels detection and cardiac interventricular septum tissue Doppler echocardiographic evaluation of women with polycystic ovary syndrome

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Introduction

The aim of this study, left ventricular systolic and diastolic function by echocardiography and tissue Doppler echocardiographic evaluation, serum N-terminal pro-B-type brain natriuretic peptide (NT-proBNP) levels of women with polycystic ovary syndrome (PCOS).

Materials and method

Thirty-two women with PCOS (age: 23.4–4.6 years; BMI: 23.8–4.8 kg/m²), similar age and BMI have features 30 healthy women controls involved in the study. Anthropometric features, NT-proBNP levels, HOMA-IR index, renal and hepatic function parameters, serum lipid and cholesterol levels, hormonal tests were measured. Interventricular septum was evaluated by tissue Doppler echocardiography.

Results

PCOS group had NT-proBNP (P = 0.04), total testosterone (P = 0.005), cholesterol (P = 0.02), and triglycerides (P = 0.006) levels higher than control group. Echocardiographic assessment of the interventricular septum thickness and width of the aortic root measurements levels in the PCOS group higher than the control group. Also, left ventricular mitral valve E-wave velocity (ZP = 0.035) longer than control group. PCOS group with the monoamines induced AVP (5HT: 194.18 pg AVP/mg protein and A: 199.26 pg AVP/mg protein) (II) became strongly increased.

Conclusions

Our study results have shown that NT-proBNP levels have able to a biochemical cardiac early marker of diagnosis subclinical diastolic dysfunction in younger women with PCOS.

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EP151

The effects of endocrine disruptors on the in vitro hormone regulation of rat pituitary

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Endocrine disrupter compounds (EDCs) may cause disorders and alter the normal hormone synthesis and/or release.

Aim was to investigate the effects of EDCs on normal hypophysis regulation; particularly the arginine–vasopressine (AVP) activated ACTH release from adenohypophysis cells and the monoamine activated AVP release from neurohypophysis cells.

Primary monolayer cell cultures prepared from Wistar rat hypophyses. Separated adenohypysis (AdH) and neurohypophysis (NH) tissues were dissociated by enzymatic and mechanic methods. The 14-day-old cultures were standardized for ACTH in AdH for AVP in NH cultures and for cell-viability. ACTH and AVP contents of the endocrine cells were checked and the hormone release function was challenged with an aspecific osmotic stimulus (30 mM K⁺). Untreated cultures used as control. Cultures treated with –1 1b 0.1 μg/ml EDCs (CIB, MII, DU, and PU/α with 8; (II) 10⁻⁸ M monoamines (epinephrine: A; serotonin: 5HT) alone/α with 8; and (III) the stimulant agents (AVP, monoamines) in combinations with EDCs/α with 8. ACTH and AVP and protein content was measured from supernatant media.

Results

Basal ACTH (1470 pg ACTH/mg protein) and AVP (47.25 pg AVP/mg protein) from AdH and NH respectively did not change significantly after the EDCs (I) treatment. The AVP induced ACTH release (11 750 pg ACTH/mg protein) and the monoamines induced AVP (5HT: 194.18 pg AVP/mg protein and A: 199.26 pg AVP/mg protein) (II) became strongly increased.

Conclusions

Statins are known inhibitors of HMG CoA reductase and can lower blood cholesterol levels. The same way, statins can lower blood 5HT levels, which in turn can lower blood AVP levels. Moreover, it is shown that in vitro treatment with statins in a concentration of 8 × 10⁻⁶ M decrease AVP-induced ACTH release.

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Endocrine disruptive effect of plastic byproduct bisphenol A on GH activity

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Bisphenol A (BPA) is a byproduct of polycarbonate plastic widely present in food containers. BPA is historically a known endocrine disruptor and due to its oestrogen agonist activity, BPA consumption is associated with hypothyroidism and reproductive disorder. Recent studies have shown that oestrogen antagonised GH actions. Since BPA has oestrogen agonist activity, the effect of BPA exposure on GH activity has not yet been investigated.

Aim

To study the in vivo effect of acute/chronic consumption of BPA on long body growth and in vitro effect of BPA on cellular GH signalling.

Method

CD-1 mice treated with BPA (1.75 mM orally) for 3 months starting from weaning (day 20). Body weight, tail length, and tibia length were monitored weekly. Liver tissue were collected 15 min after injection of GH or PBS.

Results

Mice given BPA in drinking water showed significant reduction in body weight from days 30 to 60 compared to control littermate. However, as result of catch-up growth, the BPA-treated mice weight became similar to control after day 60. Similar changes were observed in tibia length in which mice treated with BPA had significantly shorter tibia on days 30–50 and started to rise. Chronic treatment of BPA increased expression of SOCS2, which is a known cellular inhibitor of GH signalling.

Conclusion

In humans, there is a dramatic decrease in longitudinal bone growth, which begins during intrauterine life and is interrupted briefly at puberty. Here we found for first time that exposure to BPA, a plastic byproduct, interrupt linear growth with downregulation of GH signalling and mice exposed to BPA exhibit supranormal linear growth phenomenon known as catch-up growth. Further investigation is need to study the effect of BPA on the metabolic action of GH specially those related to body fat content and impact on increasing world epidemic of obesity.

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EP153
A possible link between LH and macrophage migration inhibitory factor levels in polycystic ovary syndrome
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Introduction
Analysis of gonadal steroid secretion in the serum of women during ovarian stimulation
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Purpose
Macrophage migration inhibitory factor (MIF) is a multi-functional cytokine which plays a role in metabolic and inflammatory processes. Increasing evidence suggests that there is a link between MIF and ovulation. We aimed to evaluate plasma MIF levels in women with polycystic ovary syndrome (PCOS) and to determine whether MIF levels differ between the follicular phase and mid-cycle of the menstrual cycle in eumenorrheic women.

Methods
Ninety women with PCOS and 80 age- and BMI-matched healthy eumenorrheic women were consecutively recruited into this prospective observational study. For all subjects, plasma MIF levels in early follicular phase were measured by ELISA; for the 40 healthy controls, MIF levels were also measured during mid-cycle of the same menstrual cycle.

Results
Plasma MIF levels were significantly higher in women with PCOS than in eumenorrheic women (14.16±1.59 ng/ml vs 10.39±0.70 ng/ml; P<0.001). MIF levels were significantly higher at mid-cycle than in the follicular phase in eumenorrheic women (11.15±0.61 ng/ml vs 10.56±0.82 ng/ml; P<0.001). MIF was positively correlated with BMI, h-CRP, and HOMA-IR in both groups. MIF was positively correlated with LH and free-testosterone only in the PCOS group. Binary logistic regression analyses revealed that the odds ratio (OR) for PCOS independently increases linearly with elevated MIF (OR=1.385, 95% CI=1.087–1.764, P=0.017).

Conclusion
MIF may play a crucial role in the reproductive system in women, including the development of PCOS and normal ovulation.

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EP154
Analysis of gonadal steroid secretion in the serum of women during ovarian stimulation
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Introduction
Biochemical follow up of the ovarian function after ovarian stimulation is required to monitor the secretion of ovarian steroids. It is important to investigate the entire ovarian steroidogenesis after the stimulation process.

Materials and methods
Fifty women (26 IVF and 24 ICSI) who underwent AMP induction (based on rFSH stimulation after GnRH agonist or antagonist) for the same cause of infertility were retrospectively involved and compared to 11 IUI (control). Oestrogens (oestrone, oestradiol, and oestriol), androgens (Δ4-androstenedione and testosterone), and progestogens (progesterone and 17 hydroxyprogesterone) were measured using immunoassay (RIA and CobasR Roche) each 48 h (days 5–13 in AMP and days 8–14 in control). Steroid profiles were characterized using mass spectrometry. Results are expressed as median values and a P<0.05 was considered significant.

Results
Steroids basal secretion was within the normal range (IVF, ICSI, and IUI respectively): oestradiol (2232, 317.5, 314 pmol/l), testosterone (1124.5, 903.5, and 1606.5 pmol/l), Δ4-androstenedione (3902, 3100, and 5618 pmol/l), 17 hydroxyprogesterone (1186, 1350, and 2397.5 pmol/l), and progesterone (1150, 1150, and 2950 pmol/l). We observed a significant increase in oestradiol (4638, 7864.5, and 1282 pmol/l) and Δ4-androstenedione (5932, 11 850, and 7477 pmol/l) (IVF, ICSI, and IUI respectively). The 48 h increase was significantly different between control and AMP for estradiol (1.5-fold for IUI, 1.8-fold for IVF, and 1.9-fold for ICSI) and Δ4-androstenedione (1.02-fold for IUI and 1.31-fold for ICSI). Testosterone, hydroxyprogesterone, and progesterone increase significantly only in the induced group, i.e. 1702.5 and 1470 pmol/l; 12 344 and 8650 pmol/l; and 2450 and 4150 pmol/l for IVF and ICSI respectively. There was no difference in the 48 h increase of those steroids between ICSI and FIV except for Δ4-androstenedione which increased (1.15-fold for FIV and 1.31-fold for ICSI).

Conclusion
rFSH treatment in AMP is likely to induce a biochemical ovarian hyperplasia. However, we have highlighted individual variations, which we are exploring by mass spectrometry.

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EP155
Lower peripheral fat persists in HIV-infected subjects despite viral suppression in the era of highly-active antiretroviral therapy
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Background
We compared body composition parameters in older HIV-positive individuals on stable antiretroviral therapy to age-matched HIV-seronegative individuals to assess whether differences in body composition parameters persist in the era of potent antiretroviral therapy.

Methods
Inclusion criteria to the ageing HIV cohort required subjects to be >40 years old and be on stable antiretroviral therapy for >6 months. Only subjects with undetectable plasma HIV RNA (<50 copies/ml) were included to eliminate the effects of uncontrolled HIV disease. Weight and height were measured in triplicate and averaged. Body composition (total fat, trunk fat, peripheral fat, lean tissue, and bone mineral content) was measured by dual-energy X-ray absorptiometry (DXA) using Lunar Prodigy scanner (GE Medical Systems, Inc., Milwaukee, WI, USA). Statistical analyses utilised were Wilcoxon’s rank-sum test, χ2 test, and multivariate linear regression.

Results
Body composition parameters from 133 HIV-positive individuals were compared to 74 HIV-seronegative controls. HIV-positive individuals were younger than HIV-seronegatives (medians: 62 vs 66 years, P<0.001), and comprised of more males (80% vs 80%, P<0.001). Among HIV-positive individuals, the median CD4 count was 510 cells/µl. HIV-positive individuals had similar BMI (25.9 kg/m2 vs 26.8 kg/m2, P=0.25), but lower total fat (medians: 20.168 g vs 24.817 g, P<0.001) which was accounted for by differences in peripheral fat (6.811 g vs 9.634 g, P<0.001) with similar truncal fat levels. In a multivariate linear regression model, HIV status was a significant risk factor for lower peripheral fat content, adjusting for age, gender, ethnicity (Caucasian or non-Caucasian), BMI and past use of zidovudine or stavudine (β = −0.08, P=0.02).

Conclusion
Infection with HIV is still characterized by differences in body composition despite use of potent antiretroviral therapy. Specifically, HIV is associated with lower peripheral fat content independent of past use of antiretroviral therapy known to cause peripheral fat loss.

Disclosure
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and urinary symptoms. These patients would potentially benefit from clinic (presumably more complicated diabetic patients) had erectile dysfunction concomitant LUTS. Overall a high proportion of men seen in a hospital diabetes

Results
60 men (mean age 64 years) answered the questions (July–Oct 14). 53% reported moderate (n = 27) or severe (n = 5) LUTS. The most commonly reported symptoms were urgency, frequency, and weak stream. Nine men said they had no partner or no opportunity for sexual activity. Of those that did have a partner (n = 51), 78% (n = 40) reported symptoms of erectile dysfunction (IIEF score < 25). Prevalence of moderate/severe LUTS in patients wishing to be sexually active but suffering from ED was 58% (n = 23) vs 27% (n = 3) in those with normal erections. Only six patients were already taking PDE-inhibitors.

Discussion
This survey has shown that of men with diabetes managed in a hospital clinic and who have partners (n = 51), 70% (n = 36) have symptoms of erectile dysfunction and aren’t on any medication for this. Of these men, 61% (n = 23) have concomitant LUTS. Overall a high proportion of men seen in a hospital diabetes clinic (presumably more complicated diabetic patients) had erectile dysfunction and urinary symptoms. These patients would potentially benefit from consideration for PDE-5 inhibitor treatment in the secondary care setting.

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EP157 Maternal obesity in pregnant rats is associated to increased levels of oestriol during early postnatal life and altered ovarian follicular development in the offspring

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Obesity during gestation has been related to predisposition to endocrine and metabolic diseases in the offspring. Regarding reproductive effects, an increase in BMI in pregnant mothers is associated with precocious puberty in their offspring. This has been replicated in animal models of high fat diet (HFD) administration to mothers. Also, gestational obesity has been associated to higher susceptibility to developing breast cancer in the offspring. As both precocious puberty and breast cancer are strongly related to higher oestrogens levels, we studied if offspring of rats exposed to a HFD had increased levels of endogenous oestriol from neonatal until adult age. In addition, we evaluated ovarian follicular development in adult rats because early exposure to oestrogens alters ovarian follicular development. Twenty-four Sprague-Dawley rats were fed with HFD (60% kcal fat, Research Diet) and control diet (12% kcal fat, Champion) 1 month previous to pregnancy, during pregnancy and during nursing. Offspring rats were killed at postnatal day (PND) 1, PND7, PND14, PND30, and PND60. We found that offspring of obese mothers had an increase in body weight from PND1 until PND60, and they had an early vaginal opening indicating precocious puberty. At PND60 the offspring of obese mothers showed less antral follicles and appearance of follicular cyst in the ovary. Female offspring of obese mothers had an increase in serum levels of oestradiol at PND1, PND7, PND14, PND30, and PND60. We also found a decrease in the expression of hepatic cyp3a in offspring of obese mothers in concordance with clear signs of hepatic steatosis. We conclude that maternal obesity alters hepatic metabolism of oestriol in the offspring leading to increased levels of endogenous oestriol. In addition, the increase in oestriol levels during early postnatal development may be responsible of altered reproductive function in the offspring of obese mothers.

Disclosure
FONDECYT grant number 11130707.

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EP158 Glucagon-like peptide-1 stimulates insulin secretion and then somatostatin secretion in rat islets

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Glucagon-like peptide-1 (GLP-1) is known to stimulate insulin and somatostatin secretion in pancreatic islet cells. The exogenous somatostatin inhibits insulin secretion, but GLP-1 increases insulin secretion in spite of stimulating somatostatin secretion from β-cell. So, we investigated whether there exists a time difference of insulin and somatostatin secretion inside the islets after GLP-1 stimulation or insulin secretion depends on secreted GLP-1 or somatostatin concentration inside the islets. We isolated pancreatic islets from five 8-week-old Sprague-Dawley rats by collagenase digestion. The islets were incubated in RPMI-1640 medium before experiments. In vitro, insulin and somatostatin measured at 5, 10, and 30 min depending on glucose (2.7, 5.5, and 16.7 mM as hypo-, normo-, and hyperglycaemic condition respectively) and GLP-1 concentrations (0, 0.1, and 10 ng/ml) from culture media using ELISA kit. Each well contained 30 islets/well. Insulin secretion showed continuously increased by time and GLP-1 concentration at any glucose concentration. Somatostatin secretion was increased significantly 10 min after GLP-1 administration at hypo- and normoglycaemia. However, in hyperglycaemia, insulin secretion showed the same pattern compared with the other glycaemic conditions, but somatostatin was maximally stimulated until 10 min and decreased after that without GLP-1 administration. Adding the GLP-1, somatostatin was increased continuously until 30 min. This suggested hyperglycaemia condition itself might need more insulin secretion in the β-cell than somatostatin secretion in δ-cell. Therefore, we observed time lag of intraislet somatostatin secretion was existed with GLP-1 stimulation. We observed GLP-1 induced insulin secretion is noted earlier in β-cell than somatostatin secretion in δ-cell of rat islets. Hyperglycaemic condition might primarily secrete insulin even though and inhibit somatostatin secretion inside the islets.

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EP159 Treatment with antifungal agents, fenhexamid and cyprodinil, resulted in an increase of cell cycle- and metastasis-related genes in an oestrogen receptor-dependent pathway in cellular and xenografted mouse models with BG-1 ovarian cancer cells

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Fenhexamid and cyprodinil are antifungal agents used in agricultural applications and present at measurable amounts in fruits and vegetables. In this study, the effects of fenhexamid and cyprodinil on cancer cell viability and metastasis were examined and the expression levels of proteins such as cyclins D1 and E, and cathepsins B and D were analysed in BG-1 ovarian cancer cells with oestrogen (E2; 10-9 M), fenhexamid or cyprodinil (10-5, 10-8 M). As results, in MTT assay, E2 as a positive control markedly increased BG-1 cell viability about five times and these antifungal agents increased BG-1 cell viability about 1.5–2 times compared to control. When the respective treatment was co-treated with ICI 182 780, an ER antagonist, BG-1 cell viability was reversed to the level of control. In wound-healing scratch assay, the scratched area was reduced by BG-1 cells treated with E2 or these antifungal agents compared with control. However, when BG-1 cells were treated with ICI 182 780, the scratched area was maintained to the level of control. Protein levels of cyclins D1 and E, and cathepsins B and D were induced by E2 and these antifungal agents, but when co-treated with ICI 182 780, the increased protein levels were reversed. In xenografted mouse models transplanted with BG-1 cells, E2 significantly increased the tumour mass formation about six times and fenhexamid also induced tumour formation about two times compared to vehicle (0.1% DMSO) during 80 days. However, fenhexamid did not increase the tumour mass formation. These results imply that the fenhexamid and cyprodinil may have disruptive effects on ER expressing cancer by alteration of cell cycle- and metastasis-related genes via ER dependent pathway. This work was supported by Basic Science Research
Environmental factors such as high meat consumption, caffeine, cigarette smoking, and endocrine disrupting chemical (EDCs) may enhance the risk of ovarian cancer. Cytochrome P450 (CYP) 1A1 may play a major role in metabolic activation of procarcinogens to carcinogens. 2,3,7,8-Tetrachlorodibenzop-dioxin (TCDD) is a commonplace pollutant and a promoter of carcinogenesis as the most potent substance. In this study, we examined the effects of TCDD in the presence of 17β-estradiol (E2) on the expressions of CYP1A1, CYP1B1, and aryl hydrocarbon receptor (AhR) by RT-PCR and western blot analysis. In addition, the cell viability by TCDD and E2 was examined in BG-1 human ovarian cancer cells by MTT assay. To evaluate the cell viability, BG-1 cells were cultured with control. Although, mRNA expression of CYP1B1 or AhR was not altered by E2 or TCDD in a time-dependent manner. Furthermore the translational level of AhR and CYP1A1 appeared to be increased by E2 or TCDD in a time-dependent manner. In xenografted mouse models transplanted with BG-1 cells, E2 treatment significantly increased the tumour mass formation about six times and TCDD also induced BG-1 cell viability about five times and TCDD also induced BG-1 cell viability by TCDD and E2 was examined in BG-1 human ovarian cancer cells by MTT assay. To evaluate the cell viability, BG-1 cells were cultured with vehicle or 100 nmol dexamethasone (Dex). Cells were harvested at the indicated time points. All experiments were carried out in triplicate. RT-PCR was carried out using predesigned TaqMan gene expression assays. PER1, PER2, CRY1, ARNTL, NR1D1, NR3C1, STAR, POMC, CRH, and actin expressions were measured by qRT-PCR on 7500 Fast Real-Time PCR System.

Methods and materials of research
The study involved 30 female patients of 18–55 years old. Examined were their stature, the spread of acne and its predominant localization, and the presence of hirsutism syndrome. Among morphometric parameters measured were the circumference of waist and hips with calculation of the waist-to-hip ratio. BMI was determined as well. All patients were tested for venous blood glucose and HbA1c. Hormonal examination included the determination of following parameters: free testosterone, prolactin, TSH, 17-oxoestradiol, DHEAS, oestradiol, progesterone, steroid-binding globulin, and anti-Mullerian hormone. Sonography of thyroid gland and pelvic organs was also performed.

Results of the survey
Study women were found to have ovarian hyperandrogenism, among different pathological conditions related to acne and acne-similar rash with the following percentage: atypical (late) forms of congenital adrenal dysfunction (27%); polycystic ovarian syndrome (20%); type 2 diabetes mellitus (17%); hypothyroidism (12%); hyperprolactinaemia (12%); early menopause (10%); and adrenal hyperandrogenism (1%). These parameters were only normal in 1% of examined subjects.

Conclusions
The background of acne and acne-similar rash changes in women of reproductive age are numerous hormonal and metabolic changes in the female organism. Not all cases of acne are accompanied with hyperandrogenism. Local treatment of acne in women should be preceded by intensive hormonal and instrumental examination of woman’s reproductive system, and determination of carbohydrate metabolism and thyroid status.

Introduction
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Liudmyla Naumova

Hormonal disorders in adult women with acne

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Introduction
Up to 30% of women of reproductive age suffer from acne. In most cases, acne leads to different reproductive disorders.

The purpose of the study
To determine the frequency of hormonal disorders in women with acne and acne-similar changes of the skin.

Methods and materials of research
The study involved 30 female patients of 18–55 years old. Examined were their stature, the spread of acne and its predominant localization, and the presence of hirsutism syndrome. Among morphometric parameters measured were the circumference of waist and hips with calculation of the waist-to-hip ratio. BMI was determined as well. All patients were tested for venous blood glucose and HbA1c. Hormonal examination included the determination of following parameters: free testosterone, prolactin, TSH, 17-oxoestradiol, DHEAS, oestradiol, progesterone, steroid-binding globulin, and anti-Mullerian hormone. Sonography of thyroid gland and pelvic organs was also performed.

Results of the survey
Study women were found to have ovarian hyperandrogenism, among different pathological conditions related to acne and acne-similar rash with the following percentage: atypical (late) forms of congenital adrenal dysfunction (27%); polycystic ovarian syndrome (20%); type 2 diabetes mellitus (17%); hypothyroidism (12%); hyperprolactinaemia (12%); early menopause (10%); and adrenal hyperandrogenism (1%). These parameters were only normal in 1% of examined subjects.

Conclusions
The background of acne and acne-similar rash changes in women of reproductive age are numerous hormonal and metabolic changes in the female organism. Not all cases of acne are accompanied with hyperandrogenism. Local treatment of acne in women should be preceded by intensive hormonal and instrumental examination of woman’s reproductive system, and determination of carbohydrate metabolism and thyroid status.
Disclosure
The authors received financial support from Hungarian Scientific Research Fund (OTKA PD-100648) and National Development Agency (KTIA-AIR-10_2012-0010).
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EP163
An information theoretic approach to GnRH signalling
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One way in which cells receive information about their environment is through hormones binding to appropriate receptors on their cell surface. Single cell measurements of signalling proteins typically reveal high cell–cell variability, raising questions about how reliably individual cells sense their environment in order to make decisions. Information theoretic approaches can be used to explore such sensing, treating cell signalling pathways as ‘noisy’ communication channels. Mutual information (MI) can be calculated between system inputs and outputs as a statistical measure of the reliability of sensing. GnRH acts via Gq/11-coupled seven-transmembrane receptors to stimulate ERK and nuclear factor of activated T-cells (NFAT), but information transfer has not previously been quantified for these (or other) hormone receptors. Here, we do so using automated fluorescence microscopy to quantify dual-phosphorylated (pp)ERK and the nuclear fraction (NF) of NFATc1-EFP as activation readouts. In gonadotroph-derived L2T2 cells, GnRH increased ppERK and NFAT-NF levels with maximal effects at 5–60 min. MI between GnRH and ppERK or between GnRH and NFAT-NF followed similar time courses but did not exceed 0.8 bits, implying that information transfer through these pathways is insufficient for an individual cell to unambiguously distinguish even two states of the environment. We also used imaging reporters for transcription activation (Egr1-driven or NFAT-RE-driven asRE/D) and again MI between GnRH and these outputs was always <0.8 bits. As a possible explanation for such unreliable sensing we consider GnRH receptor (R) number, using recombinant adenovirus to express GnRHR at sub-physiological to super-physiological levels (<20 000–200 000 sites/cell) in HeLa cells. This revealed that information transfer is indeed dependent on GnRHR number but MI values were <0.8, even at the highest GnRHR levels. Accordingly, this novel approach to quantification of information transfer suggests that individual pathways and cells are very inefficient sensors of GnRH concentration.

Disclosure
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EP164
Prevalence of vitamin D deficiency in Slovak women with polycystic ovary syndrome and its relation to metabolic and reproductive abnormalities
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Prevalence of vitamin D deficiency in Slovak women with polycystic ovary syndrome and its relation to metabolic and reproductive abnormalities

Objective
Polycystic ovary syndrome (PCOS) is the most common endocrine disorder characterised by menstrual dysfunction, infertility, presence of polycystic ovaries and biochemical and clinical hyperandrogenism affecting up to 4–18% of women of reproductive age. Vitamin D is thought to influence the development of PCOS through gene transcription and hormonal modulation of insulin metabolism and fertility regulation. The aim of this prospective case-control study was to investigate prevalence of vitamin D deficiency and its relation to clinical, anthropometrical, and biochemical findings in PCOS and controls.

Methods
25(OH)D, anthropometric, endocrine, and metabolic parameters were evaluated in 99 women with PCOS according to Rotterdam criteria and in 66 controls, recruited prospectively.

Results
There was no significant difference in 25(OH)D levels between PCOS women and controls (24.79 ± 10.77 nmol/l vs 25.07 ± 10.14 nmol/l, P = 0.868) and also in the prevalence of 25(OH)D deficiency in both groups (80% vs 70%; P = 0.138). PCOS women with metabolic syndrome (MS) had lower serum 25(OH)D compared to those without MS (20.6 ± 8.3 nmol/l vs 25.9 ± 11.3 nmol/l, P = 0.049). PCOS women with vitamin D deficiency had borderline higher serum triacylglycerides (1.44 ± 0.93 vs 1.03 ± 0.46, P = 0.051) and tended to have higher HOMA-IR (median (quartiles): 2.24 (1.38–3.51) vs 1.85 (1.04–3.68), P = 0.467) compared to PCOS with sufficient vitamin D levels. 25(OH)D correlated positively with HDL-cholesterol in all subjects (r = 0.139, P = 0.043; P adjusted for age, BMI, P adj = 0.03) and negatively with L/HFISH ratio (r = −0.211, P = 0.037) in PCOS.

Conclusions
Insulin resistance and other metabolic abnormalities in PCOS women seem to be related to PCOS rather than to vitamin D deficiency.

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EP165
Identification of p53 regulation site on the p27 promoter
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Angiogenesis is a crucial physiological phenomenon in female reproductive cycle. Our previous studies have shown that progesterone could inhibit proliferation of human umbilical vein endothelial cells (HUVEC) through a p53-dependent mechanism, by which the levels of p21 and p27 protein were increased, subsequently inhibiting the CDK2 kinase activity, and finally impaired the transition of the cell from the G1 phase to the S phase. While previous studies had clearly demonstrated that p53 protein directly activates p21 expression though binding onto the p21 promoter, the p53-regulated p27 gene expression has not been reported. Accordingly, the aim of this research was to investigate the precise binding domains of p53 protein on the p27 promoter. Luciferase assay showed that the potential p53 binding region spans on sites 258–310 upstream the start codon of the p27 gene. Within this range, there are three potential binding fragments with 70% similarity of p53 consensus binding domain and between each fragment is separated by <13 bp. Deletion or TCCT sequence replacement at the internal site of anyone of these fragments resulted in an irresponsiveness to progesterone treatment, suggesting that all these three fragments are essential for p53 protein to regulate the p27 promoter activity. Moreover, immunoprecipitation and chromatin-immunoprecipitation analysis demonstrated that both the formation of p53-progesterone receptor complex in the nucleus and the binding of progesterone receptor onto the p53 binding fragment of the p27 promoter were increased by progesterone treatment, suggesting that progesterone receptor might be also involved in the p53-regulated p27 promoter activity. To our knowledge, this is the first demonstration that progesterone up-regulated p27 expression in HUVEC through a p53-dependent pathway.

Disclosure
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Endocrine Abstracts (2015) Vol 37
The influence of late onset hypogonadism on the formation of proinflammatory cytokines imbalance in patients with obesity and type 2 diabetes
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Currently actively studied the role of certain inflammatory and proinflammatory cytokines in the pathogenesis of insulin resistance, type 2 diabetes, obesity, atherosclerosis. However, the influence of testosterone deficiency on the balance of proinflammatory cytokines is unexplored. The aim of the work was to evaluate the influence of testosterone deficiency on metabolic parameters and levels of proinflammatory cytokines in patients with obesity and type 2 diabetes.

Materials and methods
We examined the 85 male patients, aged 40–65 years with obesity and type 2 diabetes, which were divided into two groups, matched for age. The first group included 44 patients with testosterone levels above 12.1 nMl, the second – 41 men with content of hormone <12.1 nMl.

Results and discussion
Analysis of the data shows a statistically more significant BMI in the group of hypogonadal patients (BMI 42.03 ± 1.44 kg/m²), compared with eugonadal males (BMI 34.36 ± 2.12 kg/m²). Also in the second group there were a statistically significant increases in the levels of serum total cholesterol (6.64 ± 0.13 vs 5.79 ± 0.16 mMl) and triglycerides (2.31 ± 0.31 vs 1.72 ± 0.17 mMl). In estimating the concentration of TNF-a in the serum was found that its level in patients with deficiency of testosterone (6.32 ± 0.49 pg/ml) was significantly higher (P ≤ 0.05) that those without hypogonadism (4.38 ± 0.37 pg/ml). The results of the study of IL-6 showed a statistically significant increase in its content in the serum of patients with hypogonadism (5.39 ± 0.89 pg/ml) compared with patients with normal levels of testosterone (3.78 ± 0.36 pg/ml).

Conclusion
Reduced serum testosterone level is a factor contributing to manifestations of metabolic disorders and cytokine imbalance in patients with obesity and type 2 diabetes. Androgen deficiency may be regarded as an additional risk factor for cardiovascular disease and diabetes.

Disclosure
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Palmitic acid enhances TLR4 expression and promotes resistin/TLR4 signalling
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Toll-like receptor 4 (TLR4) has a critical role in innate immunity, and the activation of inflammatory pathways plays an important role in the induction of insulin resistance. Indeed, we have recently demonstrated that TLR4 is implicated in resistin-induced inflammation and insulin resistance in the hypothalamus.1 We have also shown that TLR4 is up-regulated in the hypothalamus of mice fed a high-fat diet. Here, we aim to decipher the molecular mechanisms implicated in the regulation of TLR4 expression. For this purpose, human neuroblastoma cells (SHSY-5Y) were exposed during 4 h to either palmitic acid (a saturated fatty acid) or the omega-3 polyunsaturated fatty acid docosahexaenoic acid (DHA). Cells were then treated with resistin. Firstly we analysed the effect of resistin, palmitic acid and DHA on inflammation markers. We show that only resistin was amplification of resistin effects promoting then insulin resistance at the neuronal level.

Reference

Disclosure
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Heterogeneity of human chorionic gonadotropin (hCG) in commercial preparations of hCG and human menopausal gonadotropin
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Introduction
Human chorionic gonadotropin (hCG) is a glycoprotein hormone composed by two subunits, a beta subunit common to all gonadotropins and a specific beta subunit. hCG is produced by trophoblast cells as differently glycosylated isoforms with a wide range of molecular weight, from 30 to 50 KDa (‘regular’ hCG is 37 KDa). hCG is used in the treatment of infertility. The aim of this study is to analyse and compare the composition of different commercial hCG.

Design
Three hCG preparations from pregnancy urine (50 mIU Gonasi-IBSA, 50 mIU Pregnyl-Organon, 70 mIU Sigma CO344), one recombinant (5 ng r-hCG, Ovidrel-Serono) and an urinary hMG (75–300 mIU Meropur-Ferring) were compared by 12% SDS–PAGE and western blotting using a polyclonal antibody against hCG beta subunit (Dako A0231). Different conditions were used in processing all the preparations such as denaturing and reducing samples or preserving their ‘native’ conformation. The western blotting patterns were confirmed by ConA Affinity Chromatography.

Results
Despite no particular differences were observed under denaturing-reducing conditions, we found qualitatively and quantitatively peculiar patterns under ‘native’ conditions. In the urinary hCG preparations up to three isoforms were found with different molecular weights (32, 37 and 45 KDa; n = 4). In contrast, in r-hCG four variants were found (one doublet at 31–32 KDa and a doublet more expressed at 44–45 KDa; n = 4). All preparations, including hMG, seem to contain hygroglycoylated hCG (hCG-H) of about 45 KDa which was characterized against hCG-H purified from human choriocarcinoma cell line (JEG-3) culture medium as control. ConA Affinity Chromatography confirmed that all the isoforms detected were glycosylation variants of hCG.

Conclusions
The commercial hCG and hMG preparations consist of several isoforms which differ in molecular weight and grade of glycosylation. Surprisingly, r-hCG has a wider range of glycosylated variants than urinary hCG. The peculiar signal pattern observed by western blotting demonstrates the heterogeneity of hCG in commercial preparations.

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Differential cell cycle control protein profiles characterise bronchial carcinoids sensitive to mTOR inhibitors
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Background
Bronchial carcinoids (BC) are rare neoplasm, still orphan of medical therapy, which arise from neuroendocrine cells. It has been previously demonstrated that the atypical BC human cell line NCI-H720 is sensitive to everolimus (E), an m-TOR inhibitor, in terms of cell viability reduction, with a G0 cell-cycle arrest and a Cyclin D1 protein reduction. On the contrary, the typical human BC cell line NCI-H60 is not sensitive to E, despite the Cyclin D1 reduction. The mechanisms underlying this phenomenon have not been fully clarified, yet.

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EPI70
Influence of mTOR and ERK 1/2 pathways on the IGF1 negative feedback in GH secreting pituitary adenoma cell line
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Aim
Our aim is to further investigate cell cycle mechanisms that underlie resistance to mTOR inhibitors in BC cells, in order to identify new therapeutic approaches.

Materials and methods
Human BC cell line cultures (NCI-H720 and NCI-H727 cells) were investigated by Western blot, cell viability and caspase activation assays before and after a challenge with E.

Results
Protein profiling of the main complexes regulating G0/G1 → S progression (CDK2/Cyclin E and CDK4/Cyclin D1) and CDK-inhibitors (p27 and phospho p27/SER10) was performed. At basal levels the two BC cell lines showed a different protein profile with the positive regulators of the cell cycle (Cyclin D/CDK4 and Cyclin E/CDK2) more expressed in NCI-H727 cells (resistant to E) as compared to NCI-H720 cells (sensitive to E), suggesting that in the Resistant BC cell line p27Kip1, despite being over-expressed, has an impaired function. We also found that E reduced Cyclin D/CDK4 protein complex as well and Cyclin E expression, but induced CDK2 expression, possibly explaining the escape of NCI-H727 from the antiproliferative effects of E. On the other hand, no modification of cell cycle control protein profile has been observed in NCI-H720 after treatment with E, indicating that the latter exerts its antiproliferative effects on this cell line by a cyclin-independent mechanism.

Conclusion
Our data indicate that resistance to mTOR inhibitors may be linked to a deranged cell cycle control protein profile. Therefore the characterization of these proteins may represent a putative marker of resistance to E, possibly contributing to a better patients selection for a therapeutic approach with mTOR inhibitors.

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EPI71
Role of TGFβ1 in pancreatic neuroendocrine tumour
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Introduction
Neuroendocrine tumours (NETs) are heterogeneous neoplasms arising from neuroendocrine cells spread in the respiratory and gastro-entero-pancreatic epithelium. The role of transforming growth factor beta-1 (TGFβ1) in NET biology is largely unknown. TGFβ1 signaling pathway is tumour suppressive in most non-transformed epithelial cell lines. In contrast, many human carcinomas are refractory to the growth-inhibitory effects of TGFβ1.

Aim
To understand the possible role of TGFβ1 on cell viability and apoptosis in pNETs and to evaluate whether this protein may affect the response to therapeutic molecules currently used in the management of pNETs.

Methods
20 pNETs primary cultures were treated with TGFβ1 and/or everolimus, a mTOR inhibitor. Cell viability and caspase activity were evaluated.

Results
TGFβ1 reduced cell viability and promoted apoptosis (~50%) in four pNETs. In the same group, TGFβ1 enhanced (+15%) the growth arrest induced by everolimus alone (50%). On the contrary in 16 pNETs we observed a 30% increase in cell viability and a similar decrease in caspase activation.

Conclusions
In conclusion, TGFβ1 reduces cell viability in a pNET sub-group and may cooperate with everolimus. Further studies are necessary to understand TGFβ1 related functional context in pNETs.

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EPI72
Reduction of growth and lesser utilisation of energy reserves in heroin addicted boys during pubertal development
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The secretion of leptin, an indicator of energy reserves, declines as energy stores are consumed in growth and development at puberty. The pubertal growth and development are often altered under different kinds of stresses. Usually, stress stimulates the release of cortisol, which is a labelled marker of stress. Early teens are inclined to drug abuse that may put their bodies under stress and may induce excessive secretion of cortisol. Since, sustained high levels of cortisol may affect growth rate at puberty, the present investigation examined body weight (BW), height, BMI and plasma concentrations of cortisol and leptin in non-smoking (n = 220) and heroin addicted (n = 211) boys and observed relationship between heroin addiction and circulating concentrations of leptin and cortisol during different stages of pubertal development. Data were analysed using Student’s t test, ANOVA and Pearson correlation. The mean BW, height, BMI and plasma concentrations of cortisol progressively increased throughout puberty and adolescence in both non-smoking and heroin addicted boys. The concentrations of cortisol were significantly higher during all stages of pubertal development in heroin addicted boys compared to non-smoking boys. The concentrations of leptin gradually declined through puberty in both groups but still remained markedly higher in heroin addicted boys. In non-smoking boys, cortisol and leptin concentrations were negatively correlated with each other at puberty. A position relationship was observed between heroin addiction and concentrations of cortisol and leptin at different stages of pubertal development. At the age of 20 years, non-smoking boys were ~10 kg heavier in weight and ~5 cm taller in size than heroin addicted boys. In conclusion, this study demonstrates reduction in growth and partial utilization of energy reserves in heroin addicted boys compared to non-smoking boys, who appeared to utilize all their energy reserves in attaining full growth at puberty.

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Persistent Mullerian duct syndrome (PMDS) is a rare disorder of sex development characterized by the persistence of Mullerian duct derivatives in a genotypic (46,XY) and phenotypic normally virilised male. PMDS is transmitted in an autosomal recessive manner, caused by mutations in the anti-Mullerian hormone gene or in the gene encoding the AMH receptor. The authors report a case of a male patient aged 62 years, with bipolar disorder, referred to the endocrinologist by incidental discovery of uterus and fallopian tubes during emergency laparotomy for acute peritonitis associated with Crohn’s disease diagnosed later. In the anamnesis: childbirth at home in a village, appropriate pubertal development, no history of gynecomastia; no erectile dysfunction or changes in libido; had no children although there was that intention. At the physical exam: male phenotype with normal penis but missing testicles in the scrotum; no eunuchoid proportions; no gynecomastia; hairy distribution with male pattern and male voice. MRI showed ‘uterus in middle location with normal anatomical pattern, inserted in the region of the seminal vesicles; prostate and seminal vesicles with normal characteristics; gonads in ovarian topography with uncharacteristic signal behavior for ovarian tissue, suggesting ovotestes’.

Hormonal study revealed hypergonadotrophic hypogonadism and no other abnormalities; Normal karyotype 46.XY. Normal bone densitometry. Histology of the right gonad (the patient refused removal of both gonads) showed atrophic testicular tissue with scattered microcalcifications, without signs of malignancy. The authors decided to present this case not only because of its rarity, but also to draw attention to the late diagnosis that was performed despite the presence of cryptorchidism. Early diagnosis and treatment of PMDS can reduce the risk of degeneration and testicular malignancy associated with prolonged cryptorchidism. Surgical replacement of the gonads in the scrotum does not ensure fertility if there is an abnormal connection between the testicles and the excretory ducts.

**Results**

Short stature was diagnosed in all patients, three of them received recombinant human GH. The average height was 152.5 ± 6.53 cm. None of women were obese (BMI: 24.12 ± 2.88 kg/m²). We stated primary amenorrhea in five patients, in one case premature ovarian insufficiency was observed. Chloromonegaly was found in one patient, in another case leukoplaikia vulvae was diagnosed. Sex hormone replacement therapy was used by four women, two the oldest non-treated patients suffered from osteoporosis. Hypothyroidism due to Hashimoto’s thyroiditis developed in five cases and they used levothyroxine. Diabetes mellitus (type 1 and type 2) appeared in two women. Patient with type 1 diabetes had many diabetic complications such as: coronary heart disease, cerebrovascular disease, peripheral vascular disease, sensory neuropathy, diabetic amyotrophy, glaucoma, cataract. One woman was operated because of non-functioning pituitary adenoma. Moreover other non-endocrine diseases were observed, including: coeliac disease (two cases), hypertension (three patients), mitral incompetence and tricuspid regurgitation (one woman), impaired hearing (two subjects), ectopic or horseshoe kidney (two cases). The intellectual performance was within the normal range in four women, two patients were mentally retarded.

**Conclusion**

Most of subjects with TS have hormonal disorders. Therefore, endocrine care is needed to optimise patients’ treatment.

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**EP175 Endocrine disorders in women with Turner syndrome**

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**Introduction**

Turner syndrome (TS) is the most common chromosomal abnormality in women. It occurs in 1/2500 to 1/3000 live-born females and results from a total or partial absence of the X chromosome. The clinical manifestations are diverse and TS is accompanied by multiple medical problems.

**Methods**

We analysed retrospectively six cases of women with TS aged 20–66 years, treated at Endocrinology Department between 2003 and 2014, to describe endocrine disorders in such patients. In the studied subjects, the diagnosis of TS was made in childhood (one patient), in adolescence (three cases) or in adulthood (two women), based on clinical symptoms and genetic tests.

**Results**

Most of patients with TS have hormonal disorders. Therefore, endocrine care is needed to optimise patients’ treatment.

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**EP174 47,XXY syndrome and hypogonadotropic hypogonadism: is this coincidence or a diverse spectrum of the syndrome?**

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**Introduction**

47,XXY syndrome is characterized by an extra copy of the Y chromosome in each cells of a male. It occurs in about 1/1000 of newborn boys and most males with this syndrome have normal sexual development and fertility. They tend to have tall stature and mild motor and language developmental problems. Testosterone levels are normal. Increased rate of criminal activity in XYY males was related to a lack of uncharacteristic signal behavior for ovarian tissue, suggesting ovotestes’.

Hormonal study revealed hypergonadotrophic hypogonadism and no other abnormalities; Normal karyotype 46.XY. Normal bone densitometry. Histology of the right gonad (the patient refused removal of both gonads) showed atrophic testicular tissue with scattered microcalcifications, without signs of malignancy. Surgical replacement of the gonads in the scrotum does not ensure fertility if there is an abnormal connection between the testicles and the excretory ducts.

**Results**

Increased rate of criminal activity in XYY males was related to a lack of

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**EP176 In vitro effects of aspartic acid, coenzyme Q10 and zinc on sperm function**

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**Introduction**

D-aspartic acid (D-AA) is involved in the regulation of spermatogenesis by influencing hormonal biosynthesis and secretion, resulting in an increased sperm concentration and progressive motility. Coenzyme Q10 (CoQ10) correlates positively with sperm concentration and motility at high concentrations, and it plays an antioxidant role, improving sperm motility and fertilization rate in ICSI cycles. Finally, low concentrations of zinc (Zn) have been found in azoospermic patients, while higher concentrations improve sperm motility, concentration and viability. On these premises, the aim of this study was to evaluate the in vitro effects of these three compounds on spermatogenesis.

**Methods**

We enrolled ten patients with oligo-astheno-teratozoospermia (OAT) and five normozoospermic subjects (age range: 20–45 years), without infection/inflammation of the male accessory glands, varicocele or other andrological diseases. Spermatozoa were incubated for 3 h with BWW (group A), BWW + ethanol + PBS (group A1) or D-AA (500 mg/ml), CoQ10 (40 mg/ml) and Zn (10 g/ml) (group B). After incubation, the following parameters were assessed: sperm progressive motility, non conventional sperm parameters (mitochondrial membrane potential, degree of viability and/or apoptosis, sperm DNA fragmentation, lipid peroxidation). Subsequently, sperm selection was performed by swim-up technique in all groups.

**Results**

In OAT, progressive motility and the number of motile spermatozoa recovered by swim-up increased in group B compared to groups A and A1 (P < 0.05). This was associated with an improvement of lipid peroxidation in group B vs A or A1.

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**EP177**
The effect of androgen replacement therapy on platelet aggregation in male patients with isolated hypogonadotropic hypogonadism

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**Aim**
To evaluate the effect of androgen replacement therapy on lipid profile and platelet aggregation in male patients with isolated hypogonadotropic hypogonadism (IHH).

**Material and methods**
36 male patient, mean age 32.2 (18–54) with IHH, admitted to the outpatient clinic of Endocrinology and Metabolism were included in the study. Patients in the study were divided into two groups as Testosterone (n = 18) and human chorionic gonadotropin (HCG) therapy (n = 18) groups. Total testosterone, fasting plasma glucose (FPG), alanine aminotransferase (ALT), lipid profile, mean platelet volume (MPV), platelet distribution width (PDW) and platelet count were evaluated before and after 6 months of the treatment in all patients.

**Results**
There was no statistically significant difference according to FPG, triglyceride levels, MPV and platelet counts when all patients (n = 36) were evaluated due to pre-treatment and post-treatment (P > 0.05). However, ALT and LDL levels were detected statistically significantly lower after treatment (P < 0.05). HDL, PDW and testosterone levels were significantly higher after treatment (P < 0.05). There was no significant difference due to testosterone, FPG, ALT, lipid profile, MPV, PDW and platelet levels compared according to treatment (HCG (n = 18), and testosterone replacement (n = 18)) (P > 0.05). While there was negative correlation with testosterone and ALT levels (r = −0.25, P = 0.03), positive correlation was detected between testosterone and PDW (r = 0.31, P = 0.007).

**Conclusion**
Platelets are involved in hemostatic process and have an important role in atherosclerosis and arterial thrombosis. MPV and PDW are two main platelet activation, and have recently been recognised as risk predictors of cardiovascular diseases. Our study revealed that androgen replacement therapy may have beneficial effects on lipid profile and ALT and negative effects on platelet aggregation. Therefore, we think that this situation should be taken into consideration when androgen replacement therapy is planned.

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**EP179**
Evaluation of most common symptoms and findings in Turkish adolescent girls with polycystic ovary syndrome

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**Objective**
Polycystic ovary syndrome (PCOS) is a complex endocrinopathy affecting 5–10% of women in reproductive period. Our goal is to determine which symptoms and findings are the most common in Turkish adolescents with PCOS.

**Material and method**
Ninety three adolescents (15–19 years old) who admitted to our outpatient clinic with at least one of the complaints (acne, obesity, menstrual irregularities and hirsutism) were enrolled in the study. All patients were evaluated due to both Rotterdam and NIH criteria.

**Results**
Due to Rotterdam and NIH criteria 40 (43.01%) and 32 (34.40%) of patients were diagnosed as PCOS respectively. Due to Rotterdam menstrual irregularities were 90%, hirsutism was 45%, obesity was 25% and acne was 32.5% in patients diagnosed as PCOS. Due to NIH these ratios were 96.9, 50, 25 and 31.3% respectively. Patients were divided into 12 subgroups due to combinations of complaints. Due to Rotterdam, PCOS diagnosis were 100% for menstrual irregularities and hirsutism together, 75% for menstrual irregularities and acne together, 66.7% for menstrual irregularities and obesity together, 66.7% for only hirsutism, 50% for hirsutism and acne together, 40% for only menstrual irregularities, 3.7% for only acne and 0% for only obesity. Due to NIH, PCOS diagnosis were 100% for menstrual irregularities and hirsutism together, 66.7% for menstrual irregularities and acne together, 44.4% for menstrual irregularities and obesity together, 33.3% for only hirsutism, 26.7% for only menstrual irregularities, 0% for only acne or only obesity. Eight patients were diagnosed as PCOS only due to Rotterdam.

**Conclusion**
The most common complaints in Turkish adolescents with PCOS were menstrual irregularities, hirsutism, acne and obesity in our study. According to guidelines PCOS in adolescents is based on clinical and/or laboratory hyperandrogenism together with persistent oligomenorrhea. Polycystic ovarian morphology can be a part of reproductive changes in adolescents.

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EP180
Post load insulin vs fasting levels in prediction of type 2 diabetes in women with PCOS
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Introduction
Women with polycystic ovary syndrome (PCOS) are at increased risk of developing insulin resistance (IR) and T2DM. In this study, we attempted to detect IR parameters that could be the best predictor T2DM in PCOS compared to controls.

Description of methods/design
In 130 women with PCOS (BMI = 29.7 ± 6.66 kg/m2; age: 25.6 ± 0.50 years) and 41 controls (age and BMI matched) OGTT and IVGTT (minimal model analyses) were performed. All women had normal fasting glucose, but 16 PCOS women had post load glucose level (120 min) over 7.8 mmol/l.

Results
After excluding PCOS women with IGT, there was no difference between fasting glucose, but glucose at 2 h (OGTT) were still higher in PCOS (P < 0.05). Fasting insulin was significantly higher in PCOS (PCOS vs control) (17.02 ± 1.07 vs 12.54 ± 1.72) as well as insulin at 120 min of OGTT (86.85 ± 7.18 vs 56.31 ± 10.57). There was no statistically significant difference between areas under insulin curve between two groups (10417.12 ± 33.47 vs 8098.36 ± 1098.2). Minimal model confirmed no difference in IV glucose tolerance (kg) between PCOS and controls and in acute insulin response (AIR). SI parameter of insulin sensitivity was significantly lower in PCOS (2.46 ± 0.18 vs 3.59 ± 0.39). Disposition index (DI) were significantly higher in controls (166.57 ± 13.9 vs 220.89 ± 33.47). Additional analyses of two PCOS subgroups with normal (NGT) and impaired glucose tolerance (IGT) showed: significant lower SI in IGT subgroup, not different AIR, lower DI. The best correlation with SI (from minimal model) showed OGIES (0.490, P < 0.01) (glucose 0.90 ± 120 min and insulin at 0 and 90 min), weaker correlation showed HOMA index (0.271, P < 0.01) and fasting insulin (−0.247, P < 0.01).

Conclusion
These insulin sensitivity indexes could be potentially used to identify subgroups of insulin resistant PCOS women with increased risk of T2DM. Our result suggests that indexes included basal and post load glucose and insulin constitute a more sensitive tool for screening metabolic abnormalities in PCOS.

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EP181
Ameliorated effects of allium sativum against bisphenol A-induced reproductive toxicity in male rats
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There is growing evidence that bisphenol A (BPA) may adversely affect humans. BPA is an endocrine disruptor that has been shown to be harmful in laboratory animal studies. A comprehensive literature search found 91 studies linking BPA to human health; 53 published within the last year. This body of literature is showing associations between BPA exposure and adverse perinatal, childhood, and adult health outcomes, including reproductive and developmental effects, metabolic disease, and other health effects. These studies encompass both prenatal and postnatal exposures, and include several study designs and population types. But until recently, there were relatively few studies examining the effect of BPA on sperm quality and the protective effects of antioxidants against its reproductive toxicity. Thus, present examination tests to assess powerful antioxidant garlic against BPA. Rats were assigned to one of four groups: 0 mg BPA and 0 g garlic/kg BW (control); 2 g garlic/kg BW; 40 mg BPA/kg BW; BPA plus garlic. Rats were orally administered their respective doses daily for 70 days. BPA caused deterioration in semen characteristics and histological changes in testes. Body weight, plasma acid phosphatase, LH and FSH were increased, while total proteins, testosterone and sex organs weights (testes, epididymis, prostates and seminal vesicles) were significantly decreased. BPA increased thiobarbituric acid-reactive substances (TBARS) and decreased the activities of the antioxidant enzymes. Testicular 17-ketosteroid reductase, acid phosphatase and protein content were decreased, while 17β-hydroxysteroid dehydrogenase was increased. Garlic alone reduced TBARS, induced the activities of the antioxidant enzymes and improved semen characteristics. Administration of garlic with BPA intoxicated rats reduced the testicular toxic condition, morphological and biochemical changes were brought back to normal. In conclusion, antioxidant potential of garlic, ameliorates the changes that are induced by BPA.

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EP182
Is serum estradiol really increased in patients with Klinefelter syndrome? Results from a meta-analysis study
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Background and aim
KS has been classically described as characterized by hyperestrogenism and elevated serum E2 together with increased gonadotropins and low-to-normal serum testosterone (T). In literature, data on increased serum E2 are not solid. The aim of this study is to meta-analyse data from studies evaluating serum E2 in both KS and healthy subjects (HS) in order to verify if E2 is increased in KS.

Methods
An extensive MEDLINE was performed using PubMed with the following key words: ‘KS’ and ‘E2’ or ‘T’ or ‘sex steroids’ from 1946 to January 2015 (current contents-ISI was used for searching oldest studies). All studies (case-control, case-series, case-reports) reporting E2 measurement were considered. Controlled-studies were used for meta-analysis, the others only for reviews. Only serum E2 at baseline (no ongoing treatments) was included. Meta-analysis was conducted according to the PRISMA statement using RevMan.

Results
Out of 956 articles, 26 case–control studies, 15 case-series and 21 case-reports had data on serum E2. A total of 878 KS and 1000 HS were included in the meta-analysis. Serum E2 was significantly higher in HS than in KS, with a mean difference of 7.93 pg/ml (CI: 2.24, 13.61; P = 0.006), with a χ² = 688.32 (I² = 97%). Serum T was significantly lower in KS than in HS, with a mean difference of −2.79 ng/ml (CI: −3.46, −2.11; P < 0.001), with a χ² = 198.29 (I² = 89%). Data from case-series and case-reports confirmed that E2 is not above the normal range in KS.

Conclusions
Serum E2 is not increased in KS and is significantly lower than in HS in this meta-analysis. The limits of this study are the heterogeneity of methods for steroids measurement and the lack of studies having the comparison of serum E2 between KS and HS as primary endpoint. The traditional belief that KS is associated to elevated E2 should be reconsidered together with some pathophysiological and clinical issues.

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EP183
Relationship between diabetes mellitus type 1 and male reproductive function
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Diabetes mellitus type 1 (DM1), an autoimmune disease, affects an increasing number of young men in reproductive age. It has been estimated that its
prevalence increases at a rate of ~3% per annum. Diabetes may affect male reproductive function by acting on the hypothalamic-pituitary-testicular axis, causing sexual dysfunction and disrupting male accessory gland function. According to a recent study shows that men with DM1 have a smaller number of live births than controls. Despite such evidence, little is known about sperm parameters (mainly limited to conventional sperm parameters) and other aspects of the male reproductive function in these patients. Therefore, this study was undertaken to evaluate both conventional and non-conventional sperm parameters, serum gonadotropes and didymo-epididymal ultrasound features in patients with DM1. To accomplish this, 30 patients with DM1 (aged 18–35 years) and 20 age-matched fertile healthy men were enrolled in this prospective study. Patients with diabetic neuropathy, other endocrine disorders or conditions known to alter sperm parameters were excluded from the study. Conventional sperm parameters were evaluated according to the WHO 2010 criteria. As far as non-conventional sperm parameters, mitochondrial function (mitochondrial membrane potential, MMP); apoptosis and chromatin/DNA integrity were evaluated by flow cytometry following specific staining. Serum total testosterone, 17β-oestradiol, LH, FSH and prolactin were measured in all patients and controls. Finally, testicular and epididymal morphometry was evaluated by ultrasound scan before and after ejaculation. Patients with DM1 had a significantly lower percentage of spermatozoa with progressive motility than controls. This abnormality was significantly lower in DM1 patients with long (> 10 years) than short (< 5 years) disease duration. In addition, the percentage of spermatozoa with high MMP was significantly lower in DM1 patients than in controls. This non-conventional parameter was significantly worse in patients with long or intermediate (5–10 years) vs short DM1 duration. Disease duration correlated inversely with the percentage of spermatozoa with high MMP. Patients with DM1 had a significantly higher cephalic and caudal epididymal diameters after ejaculation compared to controls, suggesting a lack of the physiological epididymal post-ejaculatory shrinkage. This aspect of the epididymal physiology was significantly more compromised in patients with long vs short disease duration. All the other parameters did not show any statistically significant difference. Finally, HbA1c did not correlate with any of the parameters evaluated. In conclusion, patients with DM1 had lower sperm progressive motility, impaired mitochondrial function (which precedes the onset of motility disturbance) and epididymal post-ejaculatory dysfunction which cannot be ascribed to androgenopathy and/or neuropathy. These findings may explain why patients with DM1 experience fertility disturbance.

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EP184
Serum dihydrotestosterone equivalent levels in women: a new index of hyperandrogenemia
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The measurement of androgens is critical for the diagnosis of polycystic ovary syndrome (PCOS) but it has been difficult based on poor specificity and sensitivity of assays in the female range. The direct total androgen activity can be measured with dihydrotestosterone equivalent concentration (DEQ) using chemically activated luciferase gene expression (CALUX) biosays. The aim of the study is to determine whether DEQ levels can be the index for hyperandrogenemia to be required for diagnosis of PCOS. The study involved 100 women with PCOS and 100 healthy women with regular menstrual cycles. The initial evaluation including case history, anthropometrical data, excess facial and body hair and two-dimensional vaginal ultrasound was assessed. All hormonal investigations (T, total testosterone; A, androstenedione; fTc, calculated free testosterone from T and SHBG; DEQ levels by CALUX bioassay) were performed. A correlation of T (r = 0.3912, P < 0.001), A (r = 0.41, P < 0.001) and fTc (r = 0.45, P < 0.001) with DEQ levels. DEQ levels were significantly higher in women with PCOS compared to controls (P < 0.05). Increased levels (95% percentile of serum levels in control women) of T, fTc, A and DEQ were noted in 73, 71, 69 and 82% in PCOS women, respectively. A total of 98% of the subjects with the highest quartile of DEQ levels had PCOS. The optimal DEQ cutoff value for predicting PCOS was 151.9 pg/ml (96.0% sensitivity, 87.0% specificity) and the area under the ROC curve was 0.97 (95% confidence interval, 0.94–0.99). The DEQ levels were correlated with ovarian volume (r = 0.51, P < 0.001) and ovarian follicle number (r = 0.58, P < 0.001), total cholesterol (r = 0.21, P = 0.001), LDL cholesterol (r = 0.16, P = 0.0022), fasting plasma insulin (r = 0.31, P = 0.002), post-load 2-h plasma insulin (r = 0.21, P = 0.034); DEQ levels may be a good indicator of hyperandrogenemia in women. We also confirm that measurement of DEQ levels in serum can be useful in making a diagnosis of PCOS.

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EP185
Eating habits of women without hormonal contraception depends on menstrual cycle - preliminary report
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Introduction
Hormonal changes during menstrual cycle among women without hormonal contraception could probably influence the food intake. Sex hormones modulate body energy expenditure by affecting hypothalamic neurohormones.

Aim
The aim of the study was to assess the way of nutrition among menstruating women without hormonal contraception, depend of menstrual cycle.

Materials and methods
77 menstruating women in age 19–26 entered the study. The way of nutrition (caloric intake, protein, fat, carbohydrates content) was assessed in each phases of menstrual cycle (menstrual phase, ovulatory phase, luteal phase). The 24 h feeding interview was used. The collected data were statistically analysed, α = 0.05.

Results
The mean of age was 22.79 ± 1.94 years. The mean of caloric intake in menstrual phase was 1825.65 ± 471.97 kcal, ovulatory phase 1842.28 ± 391.74 kcal, luteal phase 2258.82 ± 551.30 kcal. The mean fat intake in menstrual phase was 66.44 ± 27.06 g, ovulatory phase 70.32 ± 25.40 g; luteal phase 88.44 ± 40.38 g. The mean carbohydrates intake in in menstrual phase 247.89 ± 72.62 g, ovulatory phase 244.73 ± 57.54 g, luteal phase 290.18 ± 68.16 g. The statistical significance difference was observed between energy intake in particular cycle phases (P < 0.0001). Moreover the statistical significance differences were also observed between fat intake (P < 0.0001) and carbohydrate intake (P < 0.0001).

Conclusion
The way of nutrition among women without hormonal contraception depend on phases of menstrual cycle. In the luteal phase intake of carbohydrates including sugars was the highest. This observation could be helpful for maintaining a proper weight by better controlling of food intake.

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EP186
Relationship between polycystic ovary syndrome and platelet distribution width
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Purpose
Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive period, and it has been considered as a risk factor in cardiovascular disease due to increased prevalence of hypertension, dyslipidemia, obesity, and insulin resistance. Platelets have a pivotal role in the
development of atherothrombosis. Platelet distribution width (PDW) is a marker of platelet size that reflects the heterogeneity of the platelets. This arithmetic index routinely analyses as part of a whole blood count without additional costs. In this study we purposed whether PCOS associated with PDW.

Materials and methods
Cross-sectional study of 119 healthy women with regular menses and 133 women with PCOS age- and BMI-matched. Waist and hip circumferences, body fat percentage, CBC, plasma fasting glucose, insulin, high sensitive C-reactive protein (hs-CRP), lipids, and total testosterone levels were measured. In multivariate linear regression model, PCOS was defined as a dependent variable and PDW and other platelet indices such as mean platelet volume and platelet large cell ratio were determined as independent variables.

Results
PDW levels were significantly higher in the PCOS group compared with the control group (13.648 ± 0.424% vs 13.447 ± 0.489%; \( P = 0.003 \)). PDW levels were not correlated with hs-CRP, HOMA-IR, and BMI \((P > 0.005)\). According to linear regression model, only PDW was associated with PCOS \((R^2 = 0.05, \beta = 0.177, P = 0.022)\).

Conclusions
PDW levels were significantly higher in women with PCOS; however this index was correlated with neither HOMA-IR nor hs-CRP which is recognized as a cardiovascular risk factor in PCOS. PDW was associated with PCOS; however higher PDW levels cannot be considered as a cardiovascular risk factor in PCOS.

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**EP188**

### Effects of thiouracil compounds on chemically induced rat mammary gland carcinogenesis

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**Introduction**
Thyroidal status can play important role in progression mammary gland tumour growth. We have already shown that hypothyroidism induced by application of 6-n-propylthiouracil (PTU) – inhibitor of type I iodothyronine 5'-deiodinase (5'-DI) – prolonged tumour latency and reduced number, volume and burden of 1-methyl-1-nitrosourea (MNU) induced rat mammary gland tumors in Sprague–Dawley female rats. Design 4-Hydroxy-2-mercapto-6-methylpyrimidine (MTU) is a derivative of PTU, thus the effects of PTU or MTU on tumour progression as well as expression of selected nuclear receptors in MNU-induced mammary gland tumours and rat livers were investigated in this experiment. Female Sprague–Dawley rats were given 50 mg/kg MNU i.p. on 62nd, 109th, and 150th day of age. From 56th day of age, the PTU group of MNU treated rats was receiving PTU (1 mg/kg) intragastrically 3 × per week and MTU group of MNU animals 0.1% w/v of MTU in drinking water until the end of the experiment.

**Results**
Administration of PTU to MNU treated animals markedly reduced number of tumours when compared to MNU group of animals. Furthermore, we did not find any tumour in the MTU group of animals. However we have detected significantly reduced body weight when compared to PTU, untreated MNU animals and healthy control animals. Administration of MTU resulted in reduced expression of RARα, RXRs and increased expression of RARγ in rat liver (vs MNU and C). Using EMSA method, we have found significantly reduced amount of nuclear receptor-hormone responsive elements (RARE, TRE, and VDRE) complex in tumours of PTU treated animals (vs MNU animals). Since MTU did not affect 5'-DI in the liver, the mechanism of MTU action needs further investigation.

**Disclosure**
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**Reference**

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**EP189**

### The role of tailored treatment on conception and pregnancy at patients with insulin resistance

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Patients with insulin resistance are often confronted with conception difficulties. Our database of 1178 conceiveable female patients with metabolic disorder shows that more than 40% of them suffer from menstrual cycle disorders. More than 25% of 480 pregnant women with hyperinsulinaemia had at least one assisted reproduction procedure in their lives. 42% of patients with insulin resistance experienced missed abortion, out of them 26% one time, 12% two times. Our aim was to provide a complex and tailored treatment to women with insulin mediated metabolic disorder who desired pregnancy. The tailored treatment consisted of diet, physical exercises based on BMI and body constitution, medical treatment (if needed) and coaching. Setting BMI goals between 20 and 24, the outstanding role of dietary treatment is remarkable: patients attending (not necessarily following!) dietary counselling became pregnant up to 90%, while patients not attending these consultations were successful up to 68%. Owing to this complex and tailored method more than 71% out of 224 women became pregnant. Pregnancy rates were different according to ages: 75% up to 35 years of age, getting less to 43% above 40 years of age. During pregnancy the complex tailored treatment continued. GDM occurred in 39%of the cases. Mothers with former PCOS developed GDM up to 36%. The average birth weight of the babies was 3321 g. The complex tailored treatment requires a close follow-up and interactive cooperation.

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EP190
Eating pattern does not depend on the menstrual cycle phase in a group of women taking hormonal contraceptives: preliminary reports
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Introduction
Sex hormones, such as estrogens or progesterone may have, both directly and indirectly, an influence on the appetite changes in. In addition, exogenous sex hormones are commonly used as one method of contraception.

Aim
The purpose of this study was to assess whether the eating style in a group of menstruating women, taking oral hormonal contraceptives, is different in the individual menstrual cycle phases.

Material and methods
28 menstruating women taking oral hormonal contraceptives in age 19–25 were included to the study. The way of nutrition (caloric intake, protein, fat, and carbohydrates content) was assessed in each phases of menstrual cycle (menstrual phase, ovulatory phase, and luteal phase). The 24 h feeding interview was used. The collected data were statistically analyzed, α = 0.05.

Results
The average age of surveyed women was 22.04 ± 1.86 years. The average daily energy consumption was in the: menstrual phase 1841.76 ± 501.36 kcal; ovulatory phase 2052.58 ± 473.74 kcal. The average fat content was in the: menstrual phase 28.69 ± 70.77 g; ovulatory phase 31.46 ± 79.88 g; and luteal phase 65.88 ± 79.88 g. The average saccharose content was in the: menstrual phase 28.10 ± 27.75 g; ovulatory phase 27.75 ± 39.11 g and luteal phase 64.28 ± 39.11 g. The saccharose content was statistically significantly different between the menstrual phase and the luteal phase (P = 0.0077) and the ovulatory phase and the luteal phase (P = 0.0255). The average daily energy consumption was not statistically significantly different in the individual cycle phases (P = 0.0572). Furthermore, there was not statistically significant differences between fat content (P = 0.1178) and carbohydrates content (P = 0.1797) between the individual menstrual cycle phases.

Conclusion
Oral hormonal contraceptives does not influence eating pattern of the examined women.

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EP191
The PCOS demographic in a dedicated University Hospital Clinic
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This retrospective review of all adult women referred to a dedicated University Clinic for presumed polycystic ovarian syndrome (PCOS) aims to determine i) the true PCOS prevalence and ii) to evaluate baseline demographics by diagnostic criteria and their relationship to metabolic and cardiovascular risk parameters. All charts were reviewed. The diagnosis of PCOS rests on excluding another endocrinopathy, and fulfilling any two of the three criterias as per the Rotterdam statement, i.e. oligomenorrhea, hyperandrogenism, and/or polycystic ovaries. We reviewed coexistent hypertension, dyslipidaemia, dysglycaemia, metabolic syndrome (MetS), and NAFLD in the proven PCOS cohort. The cohort was also divided into three groups based on their inclusion criteria: group 1 (oligomenorrhea and hyperandrogenism), group 2 (oligomenorrhea and polycystic ovaries), and group 3 (hyperandrogenism and polycystic ovaries) and these factors assessed per category. 250 women were referred with a presumed diagnosis of PCOS. 134 (54%) had confirmed PCOS. The other 116 (46%) included eutopic Cushing’s, polactinoma, nonclassical CAH, PHE, POH, hypothalamic, and obesity driven oligomenorrhea. The PCOS cohort had a mean systolic BP 124.78 (s.d. 15.8) and a mean diastolic BP 75.46 (s.d. 9.4). Mean age was 27.74 years (s.d. 6.7 years). Mean BMI was 31 (s.d. 8.34). 30.4% of the PCOS group were normal weight or underweight (BMI <24.9). 71.6% had a BMI >24.9 (21.6% overweight and 48% obese). Metabolic datasets were incomplete but 2.5% had pre-diagnosed DM2 and one patient was diagnosed at presentation. 9/54 patients evaluated had ALT >40U/L. 120 patients met group 1 criteria, six met group 2 criteria, and four met group 3 criteria and 14 patients only met all three. 124/34 PCOS women had hyperandrogenism either biochemically alone (8), phenotypically alone (4) but most (113) having both. Hypertension was more prevalent in group 2 (29/120 vs group 3 2/116; p = 0.004). The BMI range was higher in group 1 (31.42 ± 2.82) and group 3 (33.89 ± 4.77) vs group 2 (25.52 ± 5.59) raising a question of a relationship to hyperandrogenism. Equally group 1 were more likely to have ↑ Tg levels (18/120 vs 1/6 vs 0/43), ↑ HDL (30/120 vs 1/8 vs 1/6) and MetS (10/120 vs 1/6 vs 0/6). 38 women having a BMI <25 had no hypertension or MetS. Of 60 women with a BMI >35, 13 had hypertension and 11 had MetS. This is the first review of an Irish cohort. It is striking that 30% of proven PCOS patients have a normal BMI undermining the assumption of obesity as a prerequisite phenotype. 90% were diagnosed with oligomenorrhea and hyperandrogenism alone. In keeping with the existing literature, this cohort has greatest metabolic risk mandating focused risk assessment and intervention. Our data was weakened by sporadic metabolic testing but nonetheless supports new guidelines recommending this. Finally, our results reiterate the principle of PCOS as a diagnosis of exclusion with almost 50% having a different underlying diagnosis.

Disclosure
Student research grant of 2000 euros from the Irish Endocrine Society.

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EP192
Hypercoagulable overall haemostatic potential is not intrinsically associated with PCOS but worsens with increasing BMI
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Introduction
Growing evidences imply a role of coagulation system in the development of thromboembolic events and progression of atherosclerosis in PCOS. The aim of the study was to identify potential relationship of overall haemostatic potential (OHP) with a syndrome per se, BMI and androgens. OHP has not yet been assessed in PCOS.

Methods
In 89 women with PCOS aged 30.9 ± 8.1 years (50 obese, 13 overweight, and 27 normal weight) and 21 healthy age matched controls (11 obese and ten normal weight) OHP with overall coagulation potential (OCP) and overall fibrinolytic potential (OFP) was determined spectrophotometrically by repeated fibrin formation and degradation registration in two parallel plasma samples. OHP was calculated as ((OCP – OHP)/OCP) × 100 (%). Results OHP increased with BMI in PCOS (15.5 ± 3.8 in obese, 12.5 ± 5.1 in overweight, and 9.6 ± 2.3 Abs-sum in normal weight) and in controls (17.3 ± 4.6 in obese and 9.1 ± 1.0 in normal weight). There was significant difference between obese and normal weight PCOS (P <0.001) and between obese and normal weight controls (P <0.001). OCP also increased with BMI in PCOS (28.5 ± 5.2 in obese vs 25.7 ± 5.2 in overweight vs 22.6 ± 3.9 Abs-sum in normal weight; P <0.001 for obese vs normal weight) and in controls (29.0 ± 7.1 in obese vs 22.3 ± 3.4 Abs-sum in normal weight, P <0.001). OCP decreased with BMI in PCOS (46.6 ± 6 in obese, 52.6 ± 6 in overweight, and 57.6 ± 6 in normal weight; P <0.001) and in controls (40.1 ± 10 in obese and 59.2 ± 3% in normal; P <0.001). OHP in healthy obese and PCOS obese did not differ significantly, while OHP for healthy obese was increased and OFP reduced in comparison to overweight and normal weight PCOS (P <0.001). Androgens did not affect OHP, OCP, and OFP.

Conclusion
PCOS was not associated with increased OHP when compared with BMI- and age-matched controls. However, increase in OHP was positively associated with BMI in PCOS and healthy women.

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**EP193**

PZ-TR: a novel human luciferase reporter cell line for assessment of thyroid receptor transcriptional activity

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Regulation of gene expression mediated by thyroid hormones (THs) plays an essential role in a variety of physiological processes. It is known that large group of natural and synthetic compounds, generally termed endocrine disruptors, can interfere with endocrine system and thus disrupt homeostasis of hormonal regulation processes in human organism. In order to screen for substances with potential disrupting effects on TH pathway, we developed and characterized human luciferase reporter gene cell line for assessment of thyroid receptor (TR) transcriptional activity – PZ-TR. PZ-TR cell line was derived from human hepatocellular carcinoma cells HepG2, which were stably transfected with reporter plasmid containing two copies of tandem thyroid response elements (TREs) upstream of reporter gene for luciferase. Dose-response analyses showed that triiodothyronine (T3), natural ligand of TR, induced luciferase activity in PZ-TR cells in dose-dependent manner and sensitivity of luciferase assays allowed detection of T3 in nanomolar range of concentrations. Maximum fold induction of luciferase activity ranged from 2.5× to almost 3× after 24 h of exposure to T3. We did not observe unspecific induction of luciferase activity by other steroid hormones and VDR ligands, only exception was partial increase of luciferase activity after treatment of PZ-TR cells with retinoic acids. Cryopreservation of PZ-TR cells did not influence their functionality, similarly responsibility to T3 and cell morphology maintained unaffected even after long-term cultivation. Novel PZ-TR cell line was used for evaluation of effects of organic tin compounds on transcriptional activity of TR. We found that both, tributyltin derivatives and triphenyltin derivatives induced luciferase activity in PZ-TR cells. These findings indicate that organic tin compounds have potential to interfere with TR-mediated regulation of gene expression and thus influence physiological activity of THs.

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Disclosure

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**EP195**

Klinefelter syndrome: a small sample retrospective analysis

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Introduction

Klinefelter syndrome (KS) is characterized by the presence of supernumerary X-chromosome and thus a 47,XXY karyotype. This syndrome remains under-diagnosed, with only about 25% of patients being identified, and only 10% during childhood.

Methods

Retrospective analysis of 11 KS patients followed-up in the Endocrinology Department of Coimbra’s Hospital and University Center. The registered data included education and occupation, time and motif of diagnosis, co-morbidities and treatment. Patients were divided in two groups: A – diagnosis at pediatric age, n=8 and B – diagnosis during adulthood, n=3.

Results

The mean age of diagnosis was 34.45±14.2 years (A – 10.5±3.1 years and B – 42.7±14.2). Group A patients were diagnosed during workup of learning disabilities; on the last evaluation five had gynecomastia (62.5%) and two osteopenia (25%), none had carbohydrate metabolism disorder; they started testosterone replacement at the age of puberty; their final height was 170.3±9.8 cm; four group A patients completed high school and one couldn’t read or write. One group B patient was diagnosed on account of infertility, and two on the workup of hypogonadotropic hypogonadism; on the last evaluation two had gynecomastia (66.7%), two osteopenia (66.7%), one osteoporosis (33.3%), two had psychiatric and behavioural disorders with cognitive impairment (66.7%), and two had diabetes mellitus with difficult metabolic control and proliferative retinopathy; their final height was 177.3±3.8 cm. One group B patient completed high school and had an occupation; the other two didn’t finish junior high school and were unemployed.

Conclusion

Cognitive impairment was found in 90.9% of patients and was the most frequent comorbidity, with educational and professional impact. Ginecomastia and osteopenia were frequent as well. Timely diagnosis can result in a better care with proper follow-up and regular screening of possible comorbidities.

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**EP196**

Endocrinopathies associated with lithium therapy in an Irish tertiary referral centre

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In patients with hypervolaeemia, 42.9% were treated with fluid restriction alone and 42.9% received diuretic and hypertonic saline. 66.7% of hypovolaemic hyponatraemia patients treated with 0.9% saline alone. Amongst 25 SIADH patients, nine responded to restriction +/− drug withdrawal alone, ten were corrected with hypertonic (1.8%) saline. Glucocorticoid replacement corrected hyponatraemia in two patients. Tolvaptan was needed in four cases. Correction of sodium ([Na+] ≥ 130 mmol/l) was achieved in 64.8% after a mean of 5 days.

Conclusion

Automatic referral to a specialist team from the laboratory was appropriate in >90% and led to a prompt diagnostic evaluation and active intervention.

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Lithium is used in psychiatric practice as maintenance therapy in bipolar disorder. It has a narrow therapeutic index with serious toxic potential. Lithium is associated with multiple endocrine and metabolic disturbances but data regarding the rates of these in individual patients is lacking. In a tertiary referral centre, all patients on lithium therapy from 2000 to 2014 were identified. The aim of this study was to assess the impact of lithium therapy on the development of endocrinopathies.

**Results**

Five hundred and eighty patients were identified across the 14-year period. The median number of serum lithium measurements per person was 5 (IQR 11) with a median duration of therapy of 4.2 years (IQR 10). Toxic lithium levels were observed in 27.8% (n = 161) of patients during follow up. Impaired renal function was more common in patients with toxic lithium levels compared to those with normal lithium levels (52.8% vs 47.2%, P < 0.001). Hypernatraemia (sodium > 145 mmol/l) was observed in 16.4% of the study population (n = 95), and it correlated with impaired renal function (r = +0.5, P < 0.001). 25.3% (n = 24) of patients who had hypernatraemia also developed hyponatraemia during the follow up period. 12/29 patients assessed with hypernatraemia had biochemical evidence of nephrogenic diabetes insipidus with a median plasma osmolality 295 mOsm/kg (IQR 17.75) and urine osmolality of 206.5 mOsm/kg (IQR 235). Impaired renal function was observed in 39% (n = 226) of the study population. 30.7% (n = 178) of patients had a TSH level > 4.2 mU/l. Serum calcium was measured in 503 patients with hypercalcaemia observed in 6.4%, 4/16 patients (25%) assessed for hypercalcaemia had elevated PTH level but all had also impaired renal function. Chronic lithium maintenance therapy and impaired renal function were risk factors for toxicity. This study highlights the multiple electrolyte and hormone disturbances observed in patients on lithium. Clinicians should be aware of this in order to monitor, detect and institute early and appropriate management of endocrinopathies.

**Conclusion**

Clinicians should be aware of this in order to monitor, detect and institute early and appropriate management of endocrinopathies.

**EP198**

**The serum AMH/total follicle count ratio is equal in women with and without PCOS**

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**Background**

Anti-Müllerian hormone (AMH) has a positive linear relationship to antral follicle count (AFC) in healthy women. However, studies of intrafollicular AMH-levels indicate a non-linear relation to AFC. It is speculated whether high AMH in polycystic ovary syndrome (PCOS) women is due to overactive follicles rather than directly reflect AFC.

**Study design**

We used data from a previous case-control study, including 262 women with prior term (controls) and preterm births (cases) in 1999–2006. Fasting blood tests, clinical and vaginal ultrasound examination were performed. The participants were categorised to have PCOS, polycystic ovary morphology (PCOM) or to be normal controls.

**Methods**

PCOS was defined according to the Rotterdam criteria. PCOM was defined as having ≥12 pre-antral follicles measuring 2–9 mm in diameter, and/or increased ovarian volume (>10 ml) in at least one ovary. We analyzed AMH/AFC ratio, adjusted for age, BMI, androstenedione, free testosterone index, and insulin.

**Main results**

AMH had a similar linear relationship to AFC in women with PCOS, PCOM, and normal controls. Other variables included in the multivariate analysis did not change this association. The AMH/AFC ratio was similar in the three groups.

**Implications of the findings**

AMH seems to be a reliable predictor of AFC independent of PCOS diagnosis or ovarian morphology. AMH can be used as a substitute indicator of AFC in most women of fertile age.

**EP199**

**Endocrine emergencies as problem in Emergency Department 6 years observation including over 200 000 admissions**

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**Introduction**

Emergencies in endocrinology often require a doctor’s high-speed operation, which is closely related to the ability to fast obtain a diagnosis. To remain a champion requires exercise. Therefore, we decided to check how often the doctors in Department of Endocrinology in Tertiary Care Hospital with Department of Endocrinology.

**Results**

In 6 years from 16th Jul 2006–15th Jul 2012 to our ED was sent or came 200 954 patients (100 727 women). From this patients 40% was sent for treatment to other departments of the hospital and 60% were treated only in the ED. Among these 120 506 patients, endocrine emergency as the main diagnosis was established in 1100 (0.9%) patients. Among patients with endocrine emergencies, the vast majority were diabetes (793 = 0.66%) and thyroid diseases (128 = 0.11%). For the remaining 179 (0.15%) patients, ED doctors established 28 different diagnoses, including seven diagnoses identified in only one patient. This means that the ED
doctors treated this patient approximately every 12 days as one of the 55 patients with other diseases. Among patients referred for treatment to other departments of the hospital with indications of endocrine emergencies only diabetes occurred relatively frequently.

Comments
We cannot exclude that part of the endocrine diseases was undiagnosed or not given as the main diagnosis. The majority of our endocrine patients are admitted elective mainly from the specialised outpatient clinics or family physicians.

Conclusion
Endocrine emergencies except diabetes and thyroid diseases are rare or very rare diseases and their diagnosis is a challenge for ED physicians. Very important, therefore, seems to be good cooperation between ED and Endocrinology Department.

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**EP200**

Thyroid abnormalities: association of thyroid autoimmunity and reproductive outcomes after IVF with thyroid autoimmunity

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Introduction
The role of thyroid hormone (T4) during embryo development is recognised as crucial. The research question of this study was if embryo quality and reproductive outcomes after IVF are affected by maternal thyroid function and/or thyroid autoimmunity (TAI).

Methods/design
We conducted a prospective study (ThyART), assessing embryo quality and reproductive outcome of women undergoing ovarian stimulation with a flexible GnRH-antagonist protocol for IVF (classic or ICSI), whose thyroid function (TSH, T4, and T3) and TAI (anti-TPO and anti-Tg) were closely observed. Embryo quality scores were calculated and reproductive outcomes were recorded.

Results
Best embryo score at day 2 was positively correlated with the overall change of T4 concentrations (r = 0.64, p = 0.048). Biochemical pregnancy and live birth rates were negatively correlated with overall change of TSH concentrations (r = -0.741, P = 0.004 and r = -0.534, P = 0.06 respectively).

Conclusion
The facts that changes in maternal TSH concentrations are associated with pregnancy outcomes and that changes in thyroid hormones are associated with embryo parameters need further confirmation. Interventional studies in women undergoing ovarian stimulation for IVF are needed to demonstrate a possible positive influence of levo-thyroxine supplementation, in selected cases, on their reproductive outcomes.

Disclosure
This work was supported by Hellenic Endocrine Society (research grant).

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**EP201**

Association of rs1800790 in fibrinogen beta polypeptide chain gene (FGB) with endometrium in Iranian women

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Background
Endometriosis is a common disease in women and considered as one of the most important reasons infertility, and it means abnormal growth of the endometrial tissue outside of the uterus. The exact prevalence of endometriosis disease is unknown. estimated that the endometriosis exists in 10% of women in productivity. Possibly, several genes interacting with each other as well as environment to result endometriosis. Given that one of the cellular pathways involved in endometriosis coagulation is since beta fibrinogen level rise increases the fibrin and it is an increasing cause of venous thrombosis? association of this gene and gene polymorphism FGB-455 (rs1800790) was examined in Iranian women.

Materials and methods
After isolation of genomic DNA from the blood lymphocytes, assessing this polymorphism was conducted by using TETRA ARMs-PCR method in 100 endometriosis patients and 100 control individuals.

Results
FGB gene polymorphism genotype frequencies were compared in the patients and control individuals. Abundance of AA, AG, and GG genotypes of the gene polymorphism FGB were 28, 48, and 24% in patients respectively, and 66, 31, and 3% in control group respectively. Results showed that there is meaningful relation between patients and control group (P = 4.619 x 10^-11).

Conclusion
Our findings showed that there was significant relationship between FGB gene polymorphism and increased risk of endometriosis in women studied. Therefore can be a determining predictive molecular biomarker identification faster and better treatment of endometriosis should be used.

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**EP202**

A haplotype of the EPCR gene is associated with a candidate risk factor for uterine myomas in Iranian women

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Introduction
Uterine myomas are the most frequent benign uterine tumours of smooth muscle cells of myometrium. Myoma is the most common uterine tumours occurring in 20–30% of women during their reproductive years. Despite this common complication of benign tumours, in most cases there are barrier of natural fertility and pregnancy continuing. Therefore, to understanding better the genetic characteristics of myoma help us in the treatment and preventive measures in these cases. The protein product of the EPCR gene activates a part of the protein C anti-coagulation pathway. The purpose of this study is to examine EPCR 4600A>G (A3 haplotype) and its relationship with uterine myoma in affected Iranian women with myoma.

Methods
In this case–control study, 100 women with myoma and 100 healthy women were studied as controls and genotype distribution of polymorphism in EPCR gene was investigated through tetra-ARMS-PCR method and the test results were analysed using χ2 test.

Results
EPCR gene polymorphism (rs867186) genotype frequencies were compared in the patients and control groups; the frequency of AA, AG, and GG genotypes were 19, 78, and 3% in the patients group and 37, 43, and 20% in the control group respectively. Results showed that there was no significant difference between patients and control group (P = 0.9).

Conclusion
The results of present study revealed that there is a possible association between the presence of C allele in EPCR gene polymorphism (rs867186) and risk of uterine myoma in Iranian population and suggests this variation as a predictor marker for estimating the risk of uterine myoma.

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**EP203**

Sexual function in women with polycystic ovary syndrome

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Objective
Poly cystic ovary syndrome (PCOS), is a common endocrine disorder in women of reproductive age, which influences metabolic, psychological and sexual aspects of their life. We aimed to evaluate the sexual function of women with PCOS in comparison with age-matched controls.

Methods
In this prospective cross-sectional study, 40 women with PCOS (mean age 27.02 ± 4.43 years) were compared with a control group of 40 healthy volunteers (mean age 25.28 ± 4.37 years). All women used barrier contraception methods at the enrolment into the study. The degree of hirsutism was assessed using the modified Ferriman–Gallwey scale. Subjects’ sexual function was evaluated using the female sexual function index (FSFI). Women were considered to be at risk for sexual dysfunction in the case of FSFI score ≤ 26.55. Testosterone and SHBG concentrations were measured by RIA Kits (DIA Source, Belgium).

Results
Mean FSFI score in women with PCOS was 24.89 ± 10.61, in the control group 27.71 ± 11.61 (P = 0.498). There were no differences in the FSFI domains scores between groups as well. 65% (n = 26) of women in PCOS and 65% (n = 26) in the control group were at risk for sexual dysfunction (P = 0.946). Non-obese PCOS women reported higher FSFI scores than obese women with PCOS (P = 0.041). FSFI scores in PCOS patients with amenorrhea (≤ 3 menstrual cycles/year) were lower if compared with patients with oligomenorrhea (4–8 cycles/year), P = 0.045. Neither testosterone concentration nor hirsutism score were related to the sexual function of the study subjects.

Conclusions
The sexual function in women with PCOS did not differ from their age-matched healthy counterparts. A high percentage of young Lithuanian women are at risk for sexual dysfunction independently of their androgen status. Clinical features of PCOS might determine sexual function in PCOS patients.

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Salivary cortisol response to psychological stress in late adolescent and young women: impact of menstrual irregularity, hirsutism, and hyperandrogenaemia

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Hyperandrogenic disorders cause psychological implication in young girls, limiting the quality of life. Salivary cortisol (SalF) testing was proved to be useful in the evaluations of acute stress responses. Aim of this study was to investigate SalF responses to a stressor event consisting in a physical examination by a trained physician for anthropometric data collection and hirsutism scoring and in a structured interview about familiar and menstrual history. Blood was collected for biochemical and hormonal evaluation. SalF and serum total testosterone (TT) were assessed by liquid chromatography–mass spectrometry. Subjects were subdivided in: menstrual irregularities group (MI, ≤ 10 bleeding/year; n = 27), isolated hirsutism group (IH, modified Ferriman–Gallwey score ≥ 8; n = 37), isolated hyperandrogenaemia group (BHA, TT > age/menstrual phase-specific cut-off; n = 11), and normal controls (NC; n = 90). Glucose, insulin, and lipid profile were normal and non different among groups. Compared to NC (21.2 ± 0.3 kg/m²), IH (22.4 ± 0.52 kg/m², P = 0.0169) and BHA (23.5 ± 0.77 kg/m², P = 0.004) displayed higher BMI; BHA also displayed higher waist circumference (75.4 ± 0.71 cm vs 81.0 ± 2.3 cm, respectively, P = 0.015). Compared to NC, IH had lower SHBG (48.11 ± 1.75 nmol/l vs 42.7 ± 2.19 nmol/l, respectively, P = 0.039). Basal SalF was not different among groups (P = 0.977); a significant SalF increase after the stressor event was observed only in ICH (1.21 ± 0.15 nmol/l vs 1.67 ± 0.23 nmol/l, P = 0.029). SalF relative increase (dSalF%) was significantly different among groups (P = 0.015); in particular, dSalF% was significantly higher in ICH compared to NC (56.1 ± 18.2% vs 3.4 ± 5.1%, respectively, P = 0.010), and this data was confirmed after adjustment for BMI, SHBG, and waist circumferences (P = 0.0051). We conclude that hirsutism, major feature of clinical hyperandrogenism but not menstrual irregularities nor hyperandrogenaemia, plays a major role in the responsiveness to stress as measured by SalF in young girls.

Disclosures
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Leptin and insulin resistance: impact on gonadal function in Algerian obese women

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Introduction
Excess of abdominal fat may disturb metabolic parameters that affect insulin level and may lead to menstrual disorders, consecutively to disturbance in sex steroids production. The aim is to link the metabolic hormones in abdominal obesity, with reproductive axis hormones in women at age. Patients and methods
85 no menopausal women aged between 17 and 52 were recruited: 62 with abdominal obesity (BMI > 30 kg/m² and waist circumference > 80) and 23 normal weight for controls (BMI < 25). Lipidemia, fasting plasma glucose, insulin, leptin, adiponectin, LH, FSH, oestiodiol (in follicular phase), progesterone (in luteal phase), 17OHOP, SDHGA, total and free testosterone using free androgen index (FAI), and sex hormone binding globulin (SHBG) were analysed. Insulin resistance and sensitivity were estimated by HOMA-IR and QUICKI indexes.

Results
Obese women show ovulation disorders (52%) type spaniomenorhormea sometimes up to amenorrhea, hirsutism (50.79%), acne (25.4%) associated to high leptin (60.91%, P < 0.001), cholesterol (17.32%, P = 0.00017), triglycerides (38.98%, P = 0.0014), LDL-c (18.80%, P = 0.0014), decreased HDL-c (17.02%, P = 0.0085), and insulin resistance (HOMA: 10.11 vs 4.39) due to decreased insulin sensitivity (QUIKI: 0.68 vs 0.83). The high levels of FSH (32.89%, P = 0.0495), oestiodiol (11.18%, P = 0.46), LH (16.93%, P = 0.349), total and free testosterone (15%, P = 0.23), and FAI (20.42%), were associated to significant rise of leptin (68.69%, P = 0.001), slight decrease of adiponectin reduced both progesterone (64.22%, P = 0.0003), 17OHOP (24.34%, P = 0.018), and DHEAS (8%, P = 0.587) as well as circulating SHBG (11.83%, P = 0.38).

Conclusion
Insulin resistance and dyslipidaemia in obese women may contribute to increase aromatase activity and decrease liver SHBG production which led to increase total and free plasma testosterone, whereas the rise of plasma gonadotropins should be consecutive to the stimulating effect of leptin on LHRH neurons. According to clinical thresholds, our results may suggest the occurrence of hyperandrogenism in obese women, but not associated with polycystic ovary syndrome.

Disclosure
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PCOS and thyroid disorder

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Background
PCOS and thyroid disorder are two of the most frequent endocrine disorder in the general population. Although, the aetopathogenesis of thyroiditis and PCOS is completely different this two entities have many features in common (cystic ovaries in hyperthyroidism and thyroid disorder in PCOS).
Objective
Our objective was to assess the increased incidence of thyroid disorder in females with PCOS.

Methods and materials
We conduct a prospective study from 2005 to 2012, 150 PCOS and 80 controls were enrolled. All patients were screened for TSH, TPO antibodies, and a clinical exam of the neck.

Results
PCOS and controls were matched for age and BMI. The mean BMI was 27.2 kg/m² and the mean age 24.5 years. The thyroid disorders were more frequent in PCOS (8.66%) than in controls (1.25%). two goitres, nine thyroiditis, and two infranodch thyroidyism (TSH >4.5 U/ml) were found in PCOS women. The TPO antibodies were positive in 6% of them and the mean level was 250 U/ml.

Discussion
In our study thyroid disorders are more frequent in PCOS women than in controls, however the prevalence (8.66%) is quite similar to the general population. Increased BMI, insulin resistance, hyperprostrogenemia, proinflammatory markers are thought to be the link between this two disorders.

Conclusion
There is enough literature report to argue that prevalence thyroid disorders is increased in PCOS women. The link between this two disorders is not elucidated.

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**EP207**

Biochemical and hormonal parameters in patients presenting with hirsutism

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Introduction
It was aimed to evaluate the biochemical and hormonal parameters in female patients with and without polycystic ovary and presenting with symptoms of hirsutism.

Materials and methods
In this study, 217 female patients presenting with symptoms of hirsutism were enrolled. Seventy-two female patients having polycystic ovaries by ultrasonography were named as group 1 and 145 female patients with normal ovaries were named as group 2. FSH, LH, plasma total and free testosterone, DHEA-S, 17-hydroxyprogesterone (17-OH Prog), glucose, homeostasis model assessment (HOMA-IR), HbA1c, total cholesterol, triglyceride, LDL cholesterol (LDL-C), and HDL cholesterol (HDL-C) were recorded.

Results
While there was statistically significant difference between total testosterone (0.62 ±0.26, 0.56 ±0.24) and LH/FSH ratio (1.54 ±1.21, 1.18 ±0.92) in groups 1 and 2 (P<0.05 in both), there were no differences among the values of free testosterone, LH, FSH, 17-OH Prog, and DHEA-S. There were no significant differences in lipid profile, glucose, insulin, HOMA-IR, HbA1c, and plasma uric acid levels. While there were positive correlations between HbA1c and total testosterone, free testosterone and HOMA-IR, HbA1c and insulin in group 1, there were negative correlations between LDL-C and total testosterone, HDL-C and free testosterone in group 2. There was a positive correlation between HOMA-IR and LH/FSH ratio only in group 2.

Conclusion
Hirsutism cases should be closely monitored in terms of metabolic parameters and cardiovascular risk factors. While evaluating hormone profile in these patients, it may be appropriate to conduct research in terms of glucose metabolism disorders and dyslipidaemia.

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**EP209**

The commonly used plasticisers (bisphenol A and phthalates) as endocrine disrupting chemicals in healthy women and women with polycystic ovary syndrome


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Plasticisers such as bisphenol A (BPA), bisphenol S (BPS), and phthalates (PAE) are commonly used in daily life in electronic equipment, cans, plastic food containers, and bottles. These substances can interact with oestrogen receptors as well as androgen receptors and therefore they are called endocrine disrupting chemicals (EDC). The aim of this study was to evaluate serum concentrations of BPA, BPS, and selected PAE in healthy women and women with polycystic ovary syndrome (PCOS). In total 191 women were studied. Eighty-six patients were diagnosed with PCOS according to the ESHRE/ASRME criteria. The healthy group consisted of 105 women without any endocrinopathies and not taking any hormonal contraceptives. Serum levels of prolactin, LH, FSH, 17OH-progesterone, total testosterone, DHEAS, insulin, and sex hormone binding globulin were measured. BPA and BPS concentration were analysed in all women’s sera using high pressure liquid chromatography method combined with mass spectrometry. Phthalates concentration were identified in biological samples using gas chromatography. Serum concentration of plasticisers were detected in 35% of samples for BPS and 90% of samples for BPA and PAEs respectively. The results of the analysis have pointed also to the higher levels of BPA in the sera of women with PCOS in comparison with healthy controls. There has been a strong positive correlation between serum concentrations of BPA and BPS with free androgen index and negative correlation with serum oestriol level. Summarising, the results for plasticisers’ concentrations and their impact on the hormonal profile confirm their endocrine disrupting potential.

Disclosure
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EP210
Serum gonadotropins secretion is not reduced with advancing age in HIV-infected females: results of a case–control study in menopausal women
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Introduction
HIV infection treated with highly active antiretroviral therapy (HAART) seems to be associated with hypogonadism in men. Less is known in HIV-infected women with gonadal status. The aim of this study is to investigate gonadal function, in menopausal HIV-infected women compared sex- and age-matched healthy subjects (HS).

Methods
We retrospectively compared 188 HIV-infected women with 192 HS selected reviewing record charts and laboratory database respectively. We considered only women older than 50 years and we grouped them according to their age (50–54; 55–59; ≥60 years). Basal serum LH, FSH, estradiol, and testosterone were measured. The FSH cut-off of 40 UI/l for establishing menopausal status.

Results
The percentage of subjects with FSH levels >40 UI/l was higher in HIV-infected women (67.5%) than in healthy controls (59.4%). This difference was found also in the younger subgroup (38% vs 27%). FSH serum levels in HIV-infected women (54.08 ± 31.47 mU/ml) did not differ (P = 0.27) from HS (50.87 ± 31 mU/ml). Accordingly, no significant differences were found in LH, estradiol, and testosterone levels.

Conclusions
Menopause seems to occur at a younger age than HS in HIV-infected women. Moreover, differently from what was documented in HIV-infected male counterpart, HIV-infected women seem to not develop hypergonadotropic hypogonadism, but have a tendency to higher serum FSH at a younger age (<54 years) suggesting premature hypergonadotropic hypogonadism. With this in view menopause may be considered an element of the process of premature aging associated with HIV infection and its comorbidities.

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EP211
Association between Apa-I polymorphism in the vitamin D receptor gene and metabolic syndrome in polycystic ovary syndrome
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Women with polycystic ovary syndrome (PCOS) have higher prevalence of metabolic disturbances such as changes in lipid profile, diabetes, hypertension and metabolic syndrome. Variants on vitamin D receptor (VDR) gene have also been related to metabolic comorbidities in general population. Therefore, the aim of the present study was to investigate whether Apa-I polymorphism (rs7974232) in the VDR gene is associated with metabolic syndrome and endocrine profile in PCOS. In this cross-sectional study 190 PCOS (Rotterdam criteria) and 100 non-hirsute and ovulatory control women were enrolled. Endocrine and clinical measurements were assessed and genotypic analyses were evaluated by real time PCR. PCOS women were younger (22.9 ± 6.7 vs 25.2 ± 7.7 years; P = 0.013) and had significantly higher BMI (29.7 ± 6.4 vs 27.0 ± 6.1 kg/m²; P = 0.001), total testosterone (0.90 ± 0.40 vs 0.54 ± 0.17 ng/ml; P < 0.001) and fasting insulin (16.87 (9.81–26.97) vs 11.09 (7.34–15.44); P < 0.001). Metabolic syndrome was present in 26.5% of PCOS and in 4.8% of controls. The genotypic distribution for Apa-I SNP in PCOS (AA: 32.1%; AC: 46.3%; CC: 21.6%) and controls (AA: 36.0%; AC: 48.0%; CC: 16.0%) was similar. PCOS participants with the CC genotype (CC vs CA + AA) of Apa-I had higher risk for metabolic syndrome (OR: 2.133; 95% CI 1.020–4.464, P = 0.042). While the analyses among control participants showed that metabolic syndrome is more frequent in CC that CA + AA genotype (13.3% vs 2.9%), no significance was found, (OR: 5.154; 95% CI 0.665–39.954, P = 0.145), maybe because of the low prevalence of metabolic syndrome in this group. The CC genotype was also associated with higher systolic blood pressure (P = 0.009), total cholesterol (P = 0.040) and LDL (P = 0.038) in both PCOS and control groups (ANOVA two-way). In conclusion, the present results suggest that variant Apa-I in VDR gene may be associated with metabolic syndrome in women with PCOS.

Disclosure
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EP212
Xbal and PvuII oestrogen receptor alpha gene polymorphism and Y chromosome deletions in infertile vs fertile men
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For the two ESR1 studied polymorphism the investigated group is in HW frequencies between the infertile patients and the control group.

Objective
The study aim to evaluate ESR1 and Y chromosome deletion in infertile men. Subjects and methods
43 infertile men, and 34 fertile men aged 20–50 years 50, were enrolled after signing the informed consent. Screening for microdeletions in the azoospermia factor (AZF) region of Y chromosome was performed by multiplex PCR and oestrogen receptor alpha gene polymorphisms (ESR1) gene polymorphisms Xbal and PvuII was performed by RFLP.

Results
In infertile patients ESR Xbal polymorphism 15 cases were wild type homoyzogote (XX), 23 heterozygote (Xx) and four mutant homozyzogote (xx). The frequency of x allele in population was 0.34, for X allele the frequency was 0.66, χ² = 1.299. In normal patients ESR Xbal polymorphism 14 cases were homoyzogote for normal allele (XX), 17 were heterozyzogote (Xx) and three were mutant homoyzogote (xx). The frequency of x allele in population was 0.45, for X allele the frequency was 0.55, χ² = 0.464. In infertile patients ESR PvuII polymorphism 12 cases were homoyzogote (PP), 22 were heterozyzogote (Pp) and eight were mutant homoyzogote (pp). The frequency of p allele was 0.45, and 0.55 for P allele, χ² = 0.137. In normal patients ESR PvuII polymorphism ten cases were homozygote for normal allele (PP), 18 were heterozyzogote (Pp) and six were mutant homoyzogote (pp). The frequency of p allele was 0.44, for P allele the frequency was 0.56, χ² = 0.184. 6.97% of all patients presented microdeletions in AZFc region and 2.32% in AZFb region. 6.1 kg/m²; P = 0.145, maybe because of the low prevalence of metabolic syndrome in this group. The CC genotype was also associated with higher systolic blood pressure (P = 0.009), total cholesterol (P = 0.040) and LDL (P = 0.038) in both PCOS and control groups (ANOVA two-way). In conclusion, the present results suggest that variant Apa-I in VDR gene may be associated with metabolic syndrome in women with PCOS.

Disclosure
This work was supported by grant from CNPq INCT 573747/2008-3, Brazil.

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EP213
The impact of adiposity on serum anti-Mullerian hormone in normal and overweight women with decreased ovarian reserve
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Background
Few previous studies suggested a negative impact of obesity on anti-Mullerian hormone (AMH) serum levels in patients with decreased ovarian reserve, but the data regarding the relationship between AMH and adiposity in the same category of patients without severe excess of body weight are scarce.

Aim
The aim of the study was to evaluate the relationship between AMH serum levels and BMI in normal weight and overweight patients with reduced ovarian reserve.

Material and methods
Patients were 196 infertile women with reduced ovarian reserve defined as AMH ≤ 1 ng/ml evaluated in a Department of Assisted Reproduction between January 2007 and January 2014. Inclusion criteria was BMI ≤ 30 kg/m². Weight, height, age and AMH was measured in all the patients.

Results
Mean age of the study group was 36.9 ± 4 years and mean BMI 21.8 ± 2.8 kg/m² (170 normal weight patients and 26 overweight patients). Serum AMH was negatively correlated with age (r = −0.134, P < 0.05) and BMI (r = −0.147, P < 0.05) when the entire group was analyzed, but the correlation was lost when only normal weight women were included in analysis. In a multivariate linear regression model both age (β = 0.0001) and BMI (β = 0.017) were independently associated with serum AMH.

Conclusion
We found that in women with decreased ovarian reserve there is a negative impact of only slightly increased adiposity on serum AMH and this effect is independent of age.

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EP215
Effects of oral contraceptives on the periodontium
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Gingivitis is the most frequent periodontal manifestation during oral contraceptives therapy, mainly due to the altered oral bacterial flora under the influence of oestrogen and progesterone. The aim of this study was to investigate the influence of low-dose oral contraceptives on periodontal health in young females.

Methods
42 women aged 18–38 years without systemic disease, non-smokers, were divided in two study groups: 22 women treated with low-dose oral contraceptives (OC) for 12 months and a control group of 20 women not using OC. Periodontal assessment included gingival index, probing depth, and attachment level at six sites per tooth. The OC users were examined before, at 6 and 12 months of therapy. The gingival index was appreciated as normal (Score 0), minimal (Score 1), moderate (Score 2) or severe (Score 3) depending on gingival colour, vascularisation, oedema, bleeding, ulceration.

Results
Pretreatment 72% had normal gingival aspect (Score 0) and 28% had a Score 1. The percentage of patients with moderate gingivitis (Score 2) was 42% at 6 months and 75% at 12 months. A severe gingival index (Score 3) was noted only at 12 months in 18% of cases. OC users at 12 months had higher gingival index scores, deeper mean probing depths (3.7 mm vs 2.4 mm; P = 0.01) and more attachment loss (2.4 mm vs 1.5 mm; P = 0.015) compared to non-users.

Conclusions
Current users of oral contraceptives had poorer periodontal health compared to non-users. Oral contraceptives may increase the risk of severe gingivitis after 12 months of use. Periodontal disease is not a contraindication for oral contraceptives, but the maintenance of a good oral hygiene should be encouraged, especially the reduction of dental plaque.

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EP216
Relationship between androgen levels and markers of endothelial dysfunction in men with type 2 diabetes
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It is well known that type 2 diabetes causes the endothelial dysfunction. However, insufficient attention is paid to the role of androgen deficiency in the formation of the early signs of endothelial dysfunction. The aim of the work was to evaluate the relationship between testosterone deficiency and markers of endothelial dysfunction in men with type 2 diabetes.

Materials and methods
We examined 88 men aged 40–65 years with type 2 diabetes. All patients were divided into two groups matched for age. The first group included 47 patients with normo-testosteronemia, the second – 41 men with testosterone concentration below 12 nmol/L. Statistical analysis was performed using analysis of the median (Me [UQ; LQ]) and comparison of two independent groups (U - Mann Whitney).

Results and discussion
We didn’t found statistically significant difference between the two groups in a concentration of E-selectin, P-selectin and VCAM-1. In the second group was found a significant increase of resistin (P = 0.01): 5.81 (5.05; 8.7) ng/ml at the interval of values (2.98–18.52) vs 4.82 (3.63; 6.34) ng/ml (0.97–13.27) and ICAM-1 (P = 0.04): 512.45 (350.1; 644.4) ng/ml vs 361.15 (256.8; 478.5) ng/ml.

Conclusion
Our results showed that assessed clinical characteristics (menstrual frequency and degree of hirsutism) are in relation to the mainly hyperandrogenic phenotypes while it was not a case for the ovarian characteristics.

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hypogonadism compared to eugonadal men (12.65 (10.9, 14.00) vs 6.62 (2.59; 8.61) mg/l) (P = 0.0001). Summary

Hypotestosteronemia in patients with type 2 diabetes increases the concentrations of markers of endothelial dysfunction and CRP level which leads to raise of cardiovascular risk in these patients. Research of resistin and ICAM-1 concentrations in patients with type 2 diabetes and androgen deficiency reveals endothelial dysfunction at the early stage.

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Disclosure

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Subclinical hypothyroidism in patients with polycystic ovary syndrome

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Objective

Polycystic ovary syndrome (PCOS) is a common endocrine metabolic disorder that affects 5–10% of women of reproductive age. In various studies, it was found to be associated with subclinical hypothyroidism. Serum TSH levels were also reported to be increased in obese individuals. In order to define the impact of obesity on the subclinical hypothyroidism observed in patients with PCOS, we aimed to investigate subclinical hypothyroidism both in lean and overweight or obese PCOS patients.

Methods

The study included 95 lean and 122 overweight or obese women with a diagnosis of PCOS defined in accordance with the Rotterdam criteria. The control group consisted of age and BMI matched healthy individuals and grouped as lean (n: 66) and or obese (n: 65) controls. Women with chronic disease such as overt hyper- or hypothyroidism, kidney or liver failure, hyperprolactinaemia, late-onset adrenal hyperplasia, and diabetes were excluded from the study. Anthropometric data (BMI and waist circumference) was recorded and hirsutism in accordance with Ferriman-Gallway index was evaluated. Plasma glucose and lipid profile, TSH, free T3, free T4, anti-thyroid peroxidase antibody, anti-thyroglobulin antibody and insulin levels were measured in all study subjects. FSH, LH, total testosterone, oestradiol and DHEA-S levels were measured in patients with PCOS.

Results

There were no significant differences between all groups with respect to glucose, free T3, free T4, anti-thyroid peroxidase antibody and anti-thyroglobulin antibody levels. Insulin and TSH levels were significantly increased in both overweight or obese women with PCOS and overweight or obese control with respect to lean groups (pinsulin: 0.001, pTSH: 0.029). But no correlation was observed between TSH levels and other studied parameters.

Conclusion

TSH elevations observed in patients with PCOS may be associated with obesity rather than the effect of PCOS.

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Subclinical hypothyroidism in young women with polycystic ovary syndrome

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Background

Separately, polycystic ovary syndrome (PCOS) and subclinical hypothyroidism (SCH) exert adverse effects on metabolic parameters. This study evaluated whether SCH in women with PCOS affects clinical, hormonal, and metabolic parameters.

Aim

To analyse the relationship between selected clinical and metabolic parameters in young women with PCOS and normal thyroid function or SCH.

Materials and methods

In this cross-sectional cohort study were enrolled 80 women diagnosed with PCOS. Their clinical, hormonal, and metabolic parameters were evaluated. SCH was defined as TSH levels of 4.5–10 mIU/l.

Results

The mean age of the 80 women was 26 ± 4.6 years. Mean BMI was 34.1 ± 6.4 kg/m². Thyroid function was normal in 64 women, and 16 had SCH. Prolactin and serum LDL cholesterol levels were significantly higher in the women with SCH (18.2 ± 6.2 ng/ml and 131.3 ± 17.4 mg/dl, respectively) compared with those with normal thyroid function (13.2 ± 9.7 ng/ml and 107.2 ± 29.4 mg/dl, respectively). No changes in other lipid profile parameters, insulin resistance or phenotypic manifestations were observed.

Conclusions

In young women with PCOS, SCH is associated with higher LDL cholesterol and prolactin levels. These two altered parameters should be considered as the SCH predictors in women diagnosed with PCOS.

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The relationships of bisphenol A levels with leptin and adiponectin in premenopausal women

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Aim

Bisphenol A (BPA) is the most common endocrine disruptor among environmental estrogens. BPA is an ingredient that is commonly used in polycarbonate plastics. In this study, our main concern is to measure the levels of BPA in premenopausal obese women and to examine the relationship of BPA with adiponectin and leptin.

Materials and methods

47 obese women and 39 non-obese healthy women were enrolled in this study. All participants were premenopausal. In this cross-sectional study, all participant’s BPA, adiponectin and leptin levels were measured. BPA levels in serum were measured by ELISA method. Obese and control group mean values were compared by t-test. BPA’s relationship with other parameters were analysed by Spearman rank correlation. The average values were presented with the standard deviation.

Results

The average age of obese premenopausal women were 34.4 and 33.4 in the control group (P=0.56). BMI mean value of the obese participants was 34.1 ± 4.0 kg/m² and the control group’s mean BMI value was 22.8 ± 1.6 kg/m² (P<0.001). BPA levels in obese women were significantly higher than the control group (1.19 ± 8.12 ng/ml, in obese and 9.5 ± 1.13 ng/ml in the control group, P=0.001). All groups in the analysis; there were a significant positive correlation between leptin and BPA levels (r=0.317, P=0.003), and a negative correlation between BPA levels and adiponectin (r=-0.269, P=0.012).

Conclusion

There are many recent studies showing the relationship between BPA and obesity. The effects of BPA that impair the regulation of body weight and lead to obesity may be related to the disruptive effects on adipocyte differentiation, fat deposition, insulin resistance and impact on the secretion of adiponectin.

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Characteristics of body composition in different phenotypes of women with polycystic ovary syndrome

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Obesity is closely associated with PCOS and worsens its metabolic and reproductive characteristics. The aim of this study was to evaluate body composition in different phenotypes of women with PCOS.
composition in different PCOS phenotypes. We evaluated 365 PCOS women (PCOS: 25.05 ± 6.24 kg/m²; 25.48 ± 5.21 years) diagnosed using ESHRE/ASRM criteria and 125 BMI-matched healthy women (Controls: 25.41 ± 5.16 kg/m²; 30.35 ± 5.62 years). PCOS were analyzed through four phenotypes: a) anovulation (ANOV), hyperandrogenism (HA), polycystic ovary morphology (PCOM), B (ANOV, HA), C (HA, PCOM) and D (ANOV, PCOM). In all subjects body composition was evaluated using bioelectrical impedance (Tanita). We analyzed basal metabolic rate (BMR), whole body fat mass (WBFFM), whole body fat free mass (WBFFM), total body water (TBW), abdominal fat mass (AFM), abdominal fat free mass (AFFM), legs fat mass (LFM). Ratio upper body (arms + abdomen)/legs fat mass was calculated.

BMI of phenotypes were: A: 25.11 ± 6.36, B: 27.03 ± 6.96, C: 25.63 ± 5.84, D: 21.41 ± 5.93 kg/m². PCOS in comparison to controls had higher WBFFM (24.42 ± 13.50 vs 18.19 ± 11.75 kg, P < 0.001), AFM (12.17 ± 7.68 vs 8.84 ± 6.59 kg, P = 0.002), LFM (4.50 ± 2.03 vs 3.84 ± 2.04 kg, P = 0.006) and ratio upper body/legs fat mass (2.80 ± 0.82 vs 2.39 ± 0.75, P = 0.007). There were no differences in BMR, WBFFM, TBW, AFFM between whole PCOS group and Controls. Phenotype D had lower BMI, WBFFM, AFM and higher LFM than all other phenotypes (P < 0.005). Phenotypes B and C had higher BMR, TBW and AFFM than phenotypes A and D and higher ratio upper body (arms + abdomen)/LFM than phenotype D (P < 0.005). Phenotype B had higher WBFFM and LFM than phenotype A (P < 0.005). Our results demonstrated that body composition could relate to the androgenic status. Accordingly, phenotype B expressed the most altered body composition structure.

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EP222
Copy number variations in the X chromosome of Klinefelter syndrome
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Introduction
Klinefelter syndrome (KS) is characterised by the presence of at least one extra X chromosome and represents the most common chromosomal aberration in men. Apart from infertility, the clinical spectrum of KS is variable and often not directly related to hypogonadism, whose expression is also not unpredictable. Several genetic mechanisms may explain the clinical features and variability of the phenotype in KS. In particular, gene-dosage effects and the parental origin of the supernumerary X chromosome in conjunction with (possibly skewed) X-chromosome inactivation may play significant roles. Here we investigated, for the first time, the genetic property of the X chromosomes by analysis of Copy Number Variations (CNV).

Materials and methods
We studied 93 non-mosaic (47,XXY) KS and 85 controls (46,XY men and 46,XX women) by SNP array using the HumanOmniexpress Bead Chip 700K (Illumina), which includes more than 700,000 SNP markers. Data generated on the Illumina Infinium platform have been analysed by the GenomeStudio software (v2011.1 (cnvpartition 3.1.6) and PennCnv.

Results
In KS the total number of CNV was 6.5/patient, significantly higher than 46,XY males (3.9 CNVs/patient) and 46,XX females (1.5 CNVs/patient). These CNV included duplications/patient and 12 deletions/patient, both significantly higher with respect to normal males and females. Also the total length of duplications and deletions, and the length of duplications and deletions per patient were significantly different from controls. After exclusion of CNV mapping to the PAR1 (69 CNVs) and PAR2 (six CNVs), regions of X–Y homology (401 CNVs), centromere (72 CNVs), and CNVs not containing genes (seven CNVs), we identified 94 CNVs in KS, ten in 46,XY men and 37 in 46,XX women. The number of deletion/patient and the length of deletion/patient were higher in KS with respect to controls. Furthermore, we identified 12 CNVs in genic regions that were patient-specific.

Conclusion
This is the first study showed the spectrum of CNVs in the X chromosomes in KS and might be important in better understanding the biology of the X chromosome in this syndrome and the role of CNVs in the genotype-phenotype relation.

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EP221
Circulating levels of FSH in men are genetically determined: study of the combined effect of polymorphisms in FSHR and FSHB genes
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Introduction
Polymorphisms in the gene for FSH receptor (FSHR) and FSH β subunit (FSHB) might modulate FSH levels and represent genetic markers for a pharmacogenetic approach to male infertility treatment. rs16616 (c.2039 A > G, Asn680Ser) and rs1394205 (c. > G > A in FSHR have been better analysed in women, whereas rs10835638 (~211 G > T) in FSHR seems to have a determinant role especially in men. However, studies considering the combined effect of these three polymorphisms have not been conducted.

Materials and methods
We studied 572 consecutive infertile males (including 93 with azoospermia-cryptozoospermia, 231 with oligozoospermia and 248 with normozoospermia) by means of semen analysis, FSH, LH, and T levels, testicular volume, and rs6166, rs1394205 and rs10835638 genotyping by RFLP and direct sequencing.

Results
The FSHR promoter polymorphism 211 G > T is significantly associated with FSH levels (9.6 ± 7.6, 7.2 ± 5.8 and 2.6 ± 1.9 IU/l respectively in men GG homozygotes, GT heterozygotes and TT homozygotes, P < 0.001). The polymorphisms ~29 G > A and Asn680Ser in FSHR taken alone were not associated with different FSH concentrations. Combined analysis of the three polymorphisms showed again that the major determinant of FSH levels is the ~211 G > T polymorphisms, only slightly modulated by the ~29G > A polymorphism, so that men with the genotype ~211 GG/ ~29 GG had the highest levels of FSH and men with the genotype ~211 TT/ ~29 AA the lowest. Polymorphism Asn680Ser in FSHR had no effect neither alone nor in combined analysed. The three polymorphisms had no effect on LH and T levels, and in accordance with this data the total number of sperm and testicular volume are modulated by the genotype. TT homozygotes for the ~211 SNP are invariably azo-o oligozoospermic with low testicular volume and FSH levels < 8 IU/l.

Conclusions
This is the first study analysing the combined contribution of the most common polymorphisms in FSHR and FSHB genes in influencing male reproductive system and showed that ~211 G > T in FSHR has a determinant role, in determining FSH levels, sperm count and testicular volume. This polymorphism alters the transcriptional activity of the gene, and therefore it determines a sort of isolated FSH deficiency with azo-o oligozoospermia and represents the ideal pharmacogenetic marker of FSH treatment.

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Calciun and Vitamin D metabolism

EP223
Development of an ELISA for the measurement of free 25OH vitamin D
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The objective of this project was to develop and characterise a simple immunoassay for the quantification of free 25-hydroxyvitamin D (25OH Vit D). Recent studies suggest that the concentration and genotype of vitamin D binding protein (DBP) are important factors that determine the bioavail-ability of 25OH Vit D in blood. It has been suggested that measurement of free, non-protein bound 25OH Vit D in serum, may provide more relevant diagnostic information than total 25OH Vit D, for instance in chronic kidney disease, bladder cancer and pancreatic cancer, or in haemodialysis patients.

A two-step enzyme-linked immunosorbent assay (ELISA) was developed for the quantification of free 25OH Vit D assay, using a highly specific anti-25OH Vit D monoclonal antibody. The assay was calibrated against a symmetric dialsis method. The calibrator range was 0–35 pg/ml. The LoB was 1.1 pg/ml, the LoD was 1.7 pg/ml. Total assay precision was 5.7% at 6.3 pg/ml, 3.8% at 15.9 pg/ml and 4.8% at 24.8 pg/ml. The assay was recently compared with calculated free 25OH Vit D in clinical populations (J. Schwartz J, Clin. Endocrinol. Metab. 2014). An assay was developed that reproducibly determines the level of free 25OH Vit D in serum. The assay...
can be used as a valuable tool in studies to establish the clinical relevance of free 25OH Vit D.

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EP224
Brown tumour in a patient with ectopic mediastinal parathyroid adenoma: a case report
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A 55-year-old Saudi woman with a complaint of anterior maxilla mass of 1 month duration. Initial examination revealed a painful mass in the anterior maxilla. Surgery was not undertaken because routine laboratory investigations revealed hypercalcemia. Initial laboratory tests performed on admission showed the following: alkaline phosphates 143 IU/l, corrected serum calcium 3.2 mmol/l, PTH 120 pmol/l. A provisional diagnosis was made for hypercalcemia due to hyperparathyroidism. Technetium thallium (99mTc-201Tb) subtraction scintigraphy (Sestamibi scanning), which demonstrated a single, ectopic anterior mediastinal parathyroid adenoma. Treatment was initiated by hydration and intravenous bisphosphonate. Initially the patient underwent extirpation of the mass and curettage of the bone. Histological sections showed multiple giant cells consistent with Brown tumour of primary hyperparathyroidism. She underwent mediastinal parathyroidectomy by median sternotomy. The post-operative course was uneventful and the patient was discharged on the 6th post-operative day without complications. Postoperative laboratory tests were normal.

Conclusions
Due to recent improvements in analytical techniques, the diagnosis of hyperparathyroidism usually occurs when the disease is in an asymptomatic phase, and the incidence of patients with advanced bone lesions is rare. The treatment of choice for bone lesions is parathyroidectomy.

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EP225
Influence of vitamin D binding protein and C3-epimer on accuracy of 25OH vitamin D ELISA assays
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The measurement of 25OH vitamin D has tremendously evolved since the first competitive protein-binding assay. Amongst the different techniques that are now routinely employed, ELISA still represents a common tool to quantify the level of 25OH Vitamin D in individuals. Several 25OH Vitamin D ELISA assays have been developed and commercialized in the last 3 years. They all differ by the antibody used and by the technology that is applied to release 25OH Vitamin D from its binding proteins. While chemiluminescence based assays (CLIA) have been extensively evaluated and compared in the literature, virtually no studies have been conducted on 25OH vitamin D ELISA assays. The performance of a 25OH Vitamin D ELISA was the only DIAsource Immunoasays ELISA was the only assay not being negatively biased by the addition of increasing amounts of DBP. Mean bias of -6 to -2% were observed with the other assays. Two assays were clearly impacted by the addition of C3-epimer, with mean positive bias of 28 and 30%. The performance of a 25OH Vitamin D immunoassay is mainly influenced by the choice of the antibody and by the efficiency of the method that is used to release 25OH Vitamin D from its binding proteins. Half of the assays involved in this study were significantly impacted by the addition of endogenous interferents. This confirms that 25OH Vitamin D remains a difficult assay.

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EP226
Pitfalls in the interpretation of bone turnover markers in liver transplantation
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Introduction
Osteoporosis and fractures are common in liver disease and fracture incidence increases after orthotopic liver transplantation (OLT). The value of bone turnover markers (BMTs) in the prediction of bone loss and fracture risk pre- and post-OLT is not known.

Study design
The BMTs PINP, osteocalcin, BALP and CTX were measured initially or in Biobank stored sera at screening and at 3, 6 and 12 months post-OLT in consecutive OLT recipients between 2008 and 2011. A prerequisite was the availability of BMD data and of spinal radiographs at screening and 6 and 12 months post-OLT.

Results
51 patients (80% male, median age 59 years) were included. Most common liver pathology was alcoholic (41%) and viral liver disease (26%). At screening, osteoporosis and osteopenia were prevalent in respectively 16 and 33% at the lumbar spine (LS) and 4 and 44% at the femoral neck (FN), and vertebral fractures were prevalent in 67%. Post-OLT, LS BMD remained stable but FN BMD decreased and 43% of patients developed new fractures. At screening, PINP and CTX levels were high and osteocalcin levels low, but only CTX levels were predictive for bone loss and fracture risk. An increase in BALP at 6 month post-OLT was predictive for fracture risk a year post-OLT.

Conclusion
Despite the many pitfalls in the interpretation of particularly collagen-derived BMTs in liver disease, high CTX levels pre-OLT and an increase in BALP post-OLT were respectively predictive for bone loss and fracture risk during the first post-OLT year.

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EP227
The evaluation of oxidative status via the measurements of total oxidant status, total anti-oxidant status, ischaemia-modified albumin and oxidised-low density lipoprotein in patients with vitamin D deficiency
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Introduction
Oxidative damage may be responsible for pathogenesis and complications of many diseases. Vitamin D deficiency has been suggested as a potential mediator of various extra-skeletal pathologies. However, there are limited data on anti-oxidant properties of vitamin D.

Methods
Forty-one subjects with vitamin D deficiency and 30 healthy controls were enrolled in the study. The levels of total anti-oxidant status (TAS), total oxidant status (TOS), ischaemia-modified albumin (IMA), oxidized-low density lipoprotein (ox-LDL), high-sensitivity C-reactive protein (hs-CRP) and fibrinogen were measured in the patient and control groups. These measurements were repeated in 17 patients after the replacement of vitamin D.

Results
Serum IMA and TAS levels were significantly higher (P < 0.001 and P = 0.035, respectively), while TAS levels were significantly lower in patients, compared with controls (P < 0.001). Additionally, fibrinogen was significantly higher in patients than controls (P = 0.003), while ox-LDL and hs-CRP levels were similar between both groups. After the replacement of vitamin D, TAS level was significantly increased (P = 0.037), and TOS and fibrinogen levels were significantly decreased (P = 0.043 and P = 0.010, respectively). Vitamin D levels were negatively correlated with IMA and fibrinogen levels (r = -0.500, P < 0.001 and r = -0.391, P = 0.002, respectively), although positively
EP228
Vitamin D status among the doctors in a tertiary referral centre in Kerala
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Vitamin D deficiency is very common in India. Doctors are vulnerable to Vitamin D deficiency since they are almost always indoors. The purpose of this study was to assess the Vitamin D status among doctors in a tertiary referral centre in Kerala, a southern state of India.

Methods
Levels of Vitamin D, calcium, phosphorus, alkaline phosphatase, and parathyroid hormone were assessed among 82 doctors and 50 healthy control subjects using Chemiluminescence immunoassay.

Results
Vitamin D deficiency (<20 ng/ml) was seen among 93.9% of the study group compared to 40% of the control group. Severe Vitamin D deficiency was seen among 54.9% of the study group and only 3.3% of control group. There was no significant correlation between the levels of vitamin D and other biochemical parameters – calcium, phosphorus, and alkaline phosphatase but there was significant negative correlation with Parathyroid hormone levels.

Conclusion
Vitamin D deficiency is highly prevalent among doctors in Southern part of India.

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EP229
The relationship between vitamin D and non-alcoholic fatty liver disease in type 2 diabetic Egyptian patients
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Background
Diabetes mellitus, hypovitaminosis D, and non-alcoholic fatty liver disease (NAFLD) are common medical conditions that share some risk factors, one of which is obesity. Both NAFLD and vitamin D deficiency have been linked to the development of metabolic syndrome and type 2 diabetes. The aim of this study is to evaluate the level of serum 25-hydroxy vitamin D (25(OH)D) in type 2 obese diabetic Egyptian patients with variable degrees of hepatic steatosis.

Methods
Sixty type 2 obese diabetic patients were recruited. BMI, HbA1c, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transferase (GGT), lipid profile, and 25(OH)D were measured. NAFLD was assessed semi-quantitatively by ultrasound on a scale of 0–3.

Results
There was a significant negative correlation between 25(OH)D and age, P = 0.027; HbA1c, P = 0.000; triglycerides (TG), P = 0.022 and degree of steatosis, P = 0.047. 25(OH)D showed a significant positive correlation with HDL, P = 0.046. ANOVA showed a significant association between the degree of steatosis and BMI, P = 0.000. Using multivariate analysis HbA1c was the only significant predictor for vitamin D level when tested with BMI and duration of diabetes, P = 0.000. Patients were divided into two subgroups according to 25(OH)D level; group 1 had normal levels, group 2 were deficient in 25(OH)D. There was a significant difference between both groups as regards age, P = 0.035; HbA1c, P = 0.000; TG, P = 0.004; and HDL, P = 0.028, with vitamin D deficient patients showing higher age, higher HbA1c, higher TG and lower HDL levels. The two groups did not differ significantly as regards the grading of hepatic steatosis.

Conclusion
Poor glycaemic control is associated with lower levels of 25(OH)D independent of BMI. Higher degrees of steatosis correlated with hypovitaminosis D.

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EP230
Study of vitamin D levels in adult males in Dakhalia Governorate
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Background
Vitamin D is a growing endemic problem. Wide proportions of healthy adults are deficient in vitamin D. It is very important for skeletal and non-skeletal health. It is now well established that many people have vitamin D levels that are less than currently recommended for optimal health.

Aim of this work
To assess vitamin-D sufficiency/deficiency in a sample of healthy Egyptian adult males in Dakhalia Governorate in Northern Egypt and correlate it to social status, sun exposure and Vitamin D intake in food.

Subjects and methods
This cross-sectional study was conducted on 90 healthy Males selected randomly from the relatives of patients in Outpatient Clinics and Internal Medicine Department of El-Gamalia General Hospital. Medical History, Dietary Questionnaire and Sun exposure Questionnaire were taken from all participants who were clinically examined as well. Laboratory investigations including hemoglobin, serum creatinine, ionized calcium were measured in all subjects and 25-(OH) vitamin D was measured in 57 subjects.

Results
Forty four out of 57 subjects (77%) had deficient vitamin D levels (<20 ng/ml), eight (14%) had insufficient levels (21–30 ng/ml) and five (9%) had sufficient levels (> 30 ng/ml). 55.6% of our subjects had moderate intake of vitamin D rich foods while 18.9% had high intake and 25.6% had low intake. Fifty three subjects had indoor occupations while 37 subjects had outdoor occupation. Sun exposure was found to be positively and significantly correlated with vitamin D levels, (R = 0.37, P value 0.005). Vitamin D was positively and significantly correlated to sun exposure in case of moderate intake of vitamin D rich foods only, (R 0.419, P value 0.021) and for indoor activities, (R 0.451, P value 0.005). Multiple regression analysis showed that intake of vitamin D rich foods was an independent predictor for vitamin D level.

Conclusion
Our results show a high rate of hypo-vitaminosis D in adult Egyptian Males in Dakhalia Governorate.

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EP231
Is there a relationship between neutrophil/lymphocyte ratio and vitamin D levels in individuals over 65 years of age?
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Introduction
Vitamin D deficiency may be an important predisposing factor for infections as well as autoimmune diseases in old individuals. Neutrophil/lymphocyte ratio (NLR), is a meaningful indicator of inflammation throughout the body. In this study we aimed to show, whether or not a relationship exists between vitamin D levels and NLR in patients older than 65 years.

Materials and method
Data of 82 patients over 65 years of age was retrospectively examined. Those without chronic renal or liver failure, active infection or disease affecting hematogram values and bone metabolism were included to study. Complete blood count and vitamin D levels of patients were recorded. NLR was calculated.

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The correlation analysis was done on patients, in order to understand whether the relationship between vitamin D levels and NLR exists.

**Results**

The mean level of vitamin D was 21.20±10.99 and NLR was 2.09±0.97. Patients were divided into four groups according to the level of vitamin D. There was not statistically significant difference between the groups in terms of NLR (P=0.433). When the patients were divided into two groups according to the adequate (>30 ng/ml) and inadequate (≤30 ng/ml) levels of vitamin D, there was not significant difference between the groups in terms of NLR (P=0.169). Significant correlation was not detected between the mean vitamin D levels and NLR in patients. There was not significant correlation between vitamin D levels and NLR, even when divided into three groups according to their age.

**Conclusions**

An important relationship between vitamin D levels and immune system function has been reported. Increase in NLR, which is an indicator of acute phase response, is associated with poor prognosis in various diseases. In our study, there was not significant relationship between vitamin D levels and NLR. However, there is no any study done on this topic in the literature. Further studies with higher number of patients may be beneficial.

**EP232**

**Relationship among plasminogen activator inhibitor-1, bone mineral density, metabolic and bone turnover markers in postmenopausal women with type 2 diabetes mellitus**

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**Background**

Women with type 2 diabetes mellitus (T2DM) have a higher risk of fractures despite increased bone mineral density (BMD). In experimental studies, a potential role of plasminogen activator inhibitor-1 (PAI-1) in bone remodelling is suggested but studies in humans are lacking. This is a first study in humans investigating whether circulating levels of PAI-1 in postmenopausal women with T2DM are related to BMD and adiposity.

**Methods**

Anthropometric variables, PAI-1 and insulin levels, serum lipids and bone turnover markers were measured in 117 postmenopausal women with T2DM. A total of 117 female patients were divided according to lumbar spine BMD measurements via dual-energy X-ray absorptiometry in three groups: 47 with osteopenia, 21 with osteoporosis and 49 with normal BMD.

**Results**

Diabetic patients with normal BMD had significantly higher BMI, greater waist circumference and lower bone turnover markers than diabetics with osteopenia and osteoporosis (P<0.01). PAI-1 was lower in diabetics with osteoporosis and osteopenia compared with diabetics with normal BMD (P<0.05). In the multiple regression models the strongest determinants of PAI-1 among metabolic parameters were triglyceride and insulin levels and the duration of T2DM, among therapy beta blockers, and among bone markers pyrilinks (P<0.05). Final regression analysis model revealed insulin (P=0.003), triglycerides levels (P=0.000002) and pyrilinks (P=0.00002) to be the strongest predictors of PAI-1 levels in all patients.

**Conclusion**

Our findings suggest that the PAI-1 has a protective effect on bone loss by suppression of bone turnover in obese diabetic patients, and the effect is primarily mediated through the influence of metabolic factors, hyperinsulinemia, hypertriglyceridemia and obesity. However, the fact that pyrilinks is also independently correlated to PAI-1 implies its direct involvement in bone metabolism influencing bone mass and strength.

**EP234**

**The effects of maternal iron status on infant fibroblast growth factor-23 and mineral metabolism**

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Fibroblast growth factor 23 (FGF23), a phosphate-regulating hormone is elevated in hypophosphataemic syndromes and is a predictor of mortality in patients with kidney disease. Recent findings demonstrate iron deficiency as a potential mediator of FGF23 expression and murine studies have shown in utero effects of maternal iron deficiency on FGF23 and phosphate (P) metabolism and bone formation (Clinkenbeard, JMEM, 2013). The aim of the current study was to investigate the impact of maternal iron status on infant mineral metabolites in mothers over the two first years of life. Infants born to mothers with normal (NI) n=25 and low (LI) n=25 iron status during pregnancy, from a mother-infant trial (ISRCTN2848550) from rural Gambia, West Africa, had blood and plasma samples analysed at 12, 24, 52, 78 and 104 weeks of life for circulating haemoglobin (Hb), C-terminal (C-FGF23; Immutopics, USA) and intact-FGF23 (I-FGF23; Kainos, Japan), P, total alkaline phosphatase (TALP) and cystatin C (Cys C) (Kone Analyser 20h, Finland). Circulating I-FGF23, P, TALP and Hb decreased and estimated glomerular filtration rate (eGFR; 74.835/cys C (mg/dl)) increased over time (mean±SD; I-FGF23: 49±13.1 to 34.3±10.9 g/ml; P: 1.86±0.13 to 1.69±0.17 mmol/l; TALP: 406±133 to 318±135 U/l, Hb: 10.7±1.6 to 9.4±1.6 g/dl and eGFR: 59.9 (11.2) to 94.5 (23.4) ml/min all P<0.0001). C-FGF23 did not change significantly over time (402±218 to 487±502 RU/ml, P=0.15). C-FGF23 and TALP were significantly higher in LI compared with NI from 52 weeks for C-FGF23 (52 weeks: 732 (702) vs 334 (225), 78 weeks: 702 (822) vs 417 (754) and 104 weeks: 628 (628) vs 347 (283) RU/ml and from 24 weeks for TALP (24 weeks: 373 (153) vs 306 (77), 78 weeks: 310 (106) vs 258 (66), 104 weeks: 340 (162) vs 289 (93) U/l). Adjusted for timepoint Hb was the strongest negative predictor of C-FGF23 concentration (Beta coefficient (s.e.) = –104.1 (27.28) RU/ml, P<0.0002; group difference P=0.03) and P the strongest positive predictor of I-FGF23 (31.4 (3.9) g/ml, P<0.0001; group difference P=0.8) and I-FGF23 did not predict C-FGF23 (r=–2.68 (3.56) RU/ml, P=0.45; group difference P=0.03). In conclusion, this study suggests that poor maternal iron
status leads to an increased infant C-FGF23 and TALP concentration in humans. Further studies are required to investigate the role of maternal iron status in the regulation of offspring FGF23 status and mineral metabolism.

Disclosure
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EP235

Vitamin D and seasonal variation among Greek female patients with osteoporosis
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Background
25 hydroxy vitamin D (25(OH)D) vitamin levels are positively associated with bone mineral density and season, time of day and sun exposure duration influence its synthesis. Variations in daylight throughout the year and zenith angle, depending on the latitude of residence, influence u.v. solar radiation which is closely related to serum 25(OH)D levels. The aim of this study was to investigate the degree of seasonal variation of 25(OH)D serum levels in a population-based cohort of postmenopausal women with osteoporosis.

Methods
Serum levels of 25(OH)D were assessed in 596 Greek patients (mean age 65.3 years old; S.D. = 9.4) in different months between August 2012 and December 2014. Each patient contributed one blood sample during the observation period and all women received vitamin D supplements as a multivitamin tablet or as a vitamin D serum levels. Although Greece is a country with sunshine, the degree of seasonal variation of 25(OH)D serum levels in a population-based cohort of postmenopausal women with osteoporosis.

Results
Serum levels of 25(OH)D were assessed in 596 Greek patients (mean age 65.3 years old; S.D. = 9.4) in different months between August 2012 and December 2014. Each patient contributed one blood sample during the observation period and all women received vitamin D supplements as a multivitamin tablet or as a 25(OH)D chewable tablet. Total hip bone mineral density was measured by dual-energy X-ray absorptiometry and all women had a T score of <2.5 or less.

Results
The minimum 25(OH)D serum level was observed in March (13.4 ± 9.5 ng/ml) and the maximum levels in August, September and October (29.1 ± 16.1; 28.9 ± 12 and 28.4 ± 8.9 ng/ml respectively). The prevalence of vitamin deficiency (<20 ng/ml), insufficiency (20–30 ng/ml) and sufficiency (≥30 ng/ml) in March was 76.5, 15.7 and 7.8% respectively. On the contrary, the highest prevalence of vitamin D sufficiency was observed in August, September and October (38.1, 45.3 and 46.5% respectively).

Conclusion
Seasonal variations should be considered when measuring and correcting vitamin D serum levels. Although Greece is a country with sunshine, the majority of postmenopausal women with osteoporosis do not reach sufficient 25(OH)D levels, regardless of type and dose of vitamin D supplementation and degree of sun exposure.

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EP236

Is vitamin D receptor gene polymorphism Taql effect the occurrence and subtype of Hashimoto’s thyroiditis?
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Background
Hashimoto’s thyroiditis is the most common autoimmune endocrine disorders and often leads to hypothyroidism. There is a relation with Vitamin D levels, vitamin D receptor (VDR) and HT reported. More than 30 gene polymorphisms are found in VDR gene. The most common four types of polymorphisms studied in autoimmune disease are FokI (exon 2), BsmI (intron 8), ApaI (intron 8) and TaqI (exon 9). The aim of this study is to investigate the association between VDR Taql gene polymorphism and HT subtypes.

Methods
We performed a case-control study that included 139 cases with HT (50 euthyroid, 50 subclinical hypothyroid, 39 overt hypothyroid patients) and 50 healthy control. Subjects were collected from Endocrinology Clinic. VDR gene polymorphisms Taql were typed by RFLP.

Results
At the Taql genotype distribution, 34% TT genotype, 38% Tt genotype and 28% tt genotype were identified in the control group. TT genotype in 46.9%, Tt genotype in 32.7% and tt genotype in 20.4% were identified in the euthyroid group. TT genotype in 55.1%, Tt genotype in 38.8% and tt genotype in 6.1% were detected in subclinical hypothyroid group. In evident hypothyroid group TT genotype in 31.6%, Tt genotype in 55.3% and tt genotype in 13.2% identified. In euthyroid group and subclinical hypothyroidism group TT genotype, in the evident hypothyroidism groups and the control group Tt genotype was detected at the highest rate.

Conclusion
Statistically significant differences was observed when all HT group compared with the control group according to Taql genotype distribution. There is relationship between VDR Taql gene polymorphism and HT. This study showed that VDR Taql gene polymorphism may be predisposed to the HT occurrence.

Disclosure
Grant numbers 2012 TPF6.

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EP237

Relation of vitamin D receptor gene polymorphism FOK-I in subtype of Hashimoto’s thyroiditis
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Background
Hashimoto’s thyroiditis is the most common autoimmune endocrine disorders and often leads to hypothyroidism. There is a relation with Vitamin D levels, vitamin D receptor (VDR) and HT reported. More than 30 gene polymorphisms are found in VDR gene. The most common four types of polymorphisms studied in autoimmune disease are FokI (exon 2), BsmI (intron 8), ApaI (intron 8) and TaqI (exon 9). The aim of this study is to investigate the association between VDR FokI gene polymorphism and Hashimoto’s thyroiditis subtypes.

Methods
We performed a case-control study that included 139 cases with HT (50 euthyroid, 50 subclinical hypothyroid, 39 overt hypothyroid patients) and 50 healthy control. Subjects were collected from Endocrinology Clinic. VDR gene polymorphisms FokI were typed by RFLP.

Results
At the FokI genotype distribution analysis, 49% of FF genotype, 36.7% of Ff genotype and 14.3% of ff genotype were detected in euthyroid Hashimoto’s thyroiditis group. The FF genotype in 46.9%, Ff genotype in 38.8% and ff genotype in 14.3% of group were detected in subclinical hypothyroidism group. In evident hypothyroidism, the FF genotype was observed in 36.8%, Ff genotype in 52.6% and ff genotype in 10.5% of the patient. In the control group, FF genotype in 58%, Ff genotype in 32% and FF genotype in 10% of the group were determined. At the FokI genotype distribution in euthyroid, subclinical hypothyroid and control groups the FF genotype was observed in the highest rate while Ff genotype was detected at the highest rate in evident hypothyroidism group. There were no statistically significant differences were observed in all Hashimoto’s thyroiditis group compared with the control group. No statistically significant difference was seen between euthyroid, subclinical hypothyroid, evident hypothyroid groups and the control group.

Conclusion
This study showed that VDR FokI gene polymorphism not affected the occurrence of the HT.

Disclosure
Grant numbers 2012 TPF6.

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EP238

Effect of supplementation with vitamin D and calcium to excessive suppression of bone metabolism during antiresorptive therapy

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Introduction
Long-term therapy with bisphosphonates is considered a risk factor for the development of atypical fractures of the femur. One of the mechanisms of these fractures is excessive suppression of bone metabolism. The supplementation dose of vitamin D and calcium could have an impact on the degree of suppression of bone turnover.

The aim
To determine whether the presence or dose of supplementation with vitamin D and calcium during antiresorptive therapy have an impact on the achieved degree of suppression of bone metabolism.

Methods and materials
This was a prospective longitudinal study that included 200 postmenopausal women with antiresorptive treatment of osteoporosis. We analysed osteocalcin, CTx and ionic calcium, before treatment and 3 months after starting the therapy, and dose of supplementation with vitamin D and calcium. Based on the values of osteocalcin and CTx after 3 months of therapy, patients were divided into four groups: Group1-accelerated bone metabolism, Group2-awaited response to therapy, Group3-excessive suppression of bone resorption, Group4-excessive suppression of bone remodeling.

Results
Calcium supplementation was carried out in 77.5% of patients, usually in a dose of 500 mg/day and vitamin D in 92.5% usually at a dose of 400 IU. The dose of calcium is satisfied recommended dose in 14% of cases, a dose of vitamin D in 42.5% of cases. Calcium supplementation was not associated with the degree of suppression of bone metabolism (P=0.557, χ2=0.155). Supplementation with vitamin D was not associated with the degree of suppression of bone metabolism (P=0.652, χ2=0.241). The values of ionic calcium before and during treatment were in the reference range.

Conclusion
Most patients with antiresorptive therapy for osteoporosis takes supplementation with vitamin D and calcium. The supplementation dose in many cases was less than the recommended dose. The degree of suppression of bone metabolism during antiresorptive therapy did not depend on the supplementation dose of calcium nor vitamin D.

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EP239

Familial hypercalcaemic hypocalcuria in a woman with Graves’ disease: a case report of mistaken identity

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We present the case of a 58 years old woman with a long history of Graves’ disease and mild hypercalcaemia (total calcium registered a maximum of 11.1 mg/dl) that was first interpreted as a consequence of hyperthyroidia. After 10 year of being treated with anti-thyroid drugs the patient finally decides to undergo surgery. Immediately after surgery this particular patient does not develop hyperthyroidism, her calcium level remaining a little high. Six weeks after surgery under appropriate thyroid supplementation the calcium levels still remains a little high (10.8 mg/dl). The labs also show normal phosphate, with normal alkaline phosphatase, normal PTH, normal renal function. Other causes of hypercalcaemia were also excluded. We raised the suspicion of a FHH although the patient did not have any familial history. We found hypercalciuria (3 mg/24 h) and a low calcium/creatinine clearance (0.002) which sustain our supposition.

After that we not have any familial history. We found hypercalciuria (3 mg/24 h) and a low calcium/creatinine clearance (0.002) which sustain our supposition. After that we not have any familial history. We found hypercalciuria (3 mg/24 h) and a low calcium/creatinine clearance (0.002) which sustain our supposition. After that we not have any familial history. We found hypercalciuria (3 mg/24 h) and a low calcium/creatinine clearance (0.002) which sustain our supposition.

We report the case of a 31-year-old woman with a previous RYGB, who suffered severe and symptomatic chronic hypercalcemia after total thyroidectomy. Six months after the surgery, corrected calcium level had severely decreased (5.2 mg/dl) and the patient related generalised muscle cramps, lappable mood and increased anxiety. She required aggressive therapy with oral calcium and calcitriol (highest dose: 12 g of calcium carbonate and 8 µg of calcitriol per day) and frequent calcium infusions, but there was no improvement in serum calcium level. Due to the lack of response to standard therapy, teriparatide treatment was started (injection with s.c. injections and thereafter with a multiphase i.e. infusion) but the results were disappointing. As there was no response to different medical treatments, reversal of RYGB was performed with no complications and a subsequent sustained increase in serum calcium level.

Conclusion
This case shows that patients with postoperative hyperparathyroidism and RYGB have increased risk of severe recalcitrant symptomatic hypercalcaemia. In our case teriparatide was ineffective but, as this is the first patient reported, more results are needed to evaluate properly the effect of teriparatide in this kind of hypercalcaemia. The reversal of RYGB may be an optimal treatment, if medical management has failed, because the surgery recovers an adequate absorption of calcium and vitamin D from previously bypassed duodenum and proximal jejunal loop.

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EP241

Hypovitaminosis D in pregnancy: can the Mediterranean paradox be explained? A systematic review

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Introduction
Despite high levels of sunshine, maternal hypovitaminosis D during pregnancy is prevalent in the Mediterranean region, consisting a paradox. The aim of the study was to systematically review trials that investigated vitamin D concentrations during pregnancy in this region, in order to determine predictors of hypovitaminosis D and explain the paradox.

Methods
After applying inclusion/exclusion criteria, 15 studies were entered into the systematic review, involving 2649 pregnant women and 1820 neonates. The main outcome was maternal vitamin D concentration. Possible predictors of the outcome included study, maternal and neonatal characteristics (age, BMI, race, socioeconomic status, skin type, gestational age, sun exposure, calcium and vitamin D intake and supplementation, smoking status, parity, season of delivery, pregnancy complications).

Results
Studies differed widely in vitamin D deficiency criteria, methods of measurement and outcomes. However, prevalence of maternal and neonatal hypovitaminosis D was very high (90%). Predictors of maternal hypovitaminosis D were dark skin phototype, race and sartorial habits. Only a few pregnant women met the recommended dietary daily intake of calcium and vitamin D. Vitamin D supplementation was not a common practice.
Conclusions
Hypovitaminosis D during pregnancy is prevalent in the Mediterranean region. Racial, social and cultural habits, as well as the absence of preventive strategies seem to negate the benefits of sun exposure.
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EP242
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Introduction
Obesity was thought to be protective against osteoporosis, but studies have shown conflicting results. We analysed the cross-sectional data from the National Health and Nutrition Examination Survey Data (NHANES) survey (2008–2012) to observe the association between BMI (BMI and/or waist circumference) and bone mineral density (BMD) at the femoral neck.

Research methods and design
We categorised the study population (women aged 50 years and above) into three groups based on their BMI- lean (BMI <18.5 kg/m²), normal (BMI between 18.6-24.9 kg/m²), and overweight/obese (BMI ≥25 kg/m²). We reviewed and tabulated data on the demographics (age, race and other covariates), waist circumference (cm), mean systolic BP (mm/Hg), HOMA insulin resistance, and total cholesterol (mg/dl). We analysed the data on femoral neck BMD (gm/cm²), total femur BMD, femoral neck bone mineral content (BMC in gm) and total femur BMC. We used the one-way ANOVA to test the difference between the groups. We also performed a correlation (non-parametric spearman’s ρ) between BMI and femoral neck BMD and waist circumference and femoral neck BMD.

Results
There were 1071 persons in the cohort. There was no significant difference in BMD or BMC between the groups at the femoral neck (P=0.39, P=0.79 respectively) or total femur (P=0.75, P=0.86 respectively). Systolic blood pressure was higher in obese/overweight women (P <0.01). There was no correlation between femoral neck BMD and BMI (spearman’s ρ =0.07, P=0.25) or femoral neck BMC and waist circumference (spearman ρ =0.09, P=0.14).

Conclusions
Our results show that BMI and waist circumference are not associated with differences in femoral neck BMD in post-menopausal women.
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EP243
The response to teriparatide of a patient with β-thalassemia and multiple endocrine complications
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Introduction
Osteopenia/osteoporosis in young adults with β-thalassemia major (BTM) is a prominent cause of morbidity despite adequate transfusion and iron chelation therapy. The reported frequency of osteoporosis, even in well treated TM patients varies from 13.6% to 50%, with an additional 45% affected by osteopenia.

Case report
We present the case of a 36-years-old male patient with BTM treated for 1 year with teriparatide for osteoporosis. Our patient was diagnosed with BTM at 6 months of age and he was treated with chronic blood transfusions since that moment associated intermittently with chelation therapy due to limited availability and lack of compliance of the patient. From his medical history we mention splenectomy at the age of 3, iron overload-related liver disease, chronic hepatitis C, cardiomegaly (hemosiderosis), femoral diaphysis fracture (1992), hyperparathyroidism (2009). For his endocrine complications he received substitutive treatment with testosterone undecanoate, calcium, vitamin D and insulin. In January 2009 he was diagnosed with severe osteoporosis with multiple vertebral fractures, he had vertebroplasty performed at T11 and T12; alendronate treatment was initiated until November 2013 when a new vertebral fracture occurred at L5. In this context, the alendronate treatment was considered suboptimal/ineffective; therefore, therapy with ipPTH was initiated. After 1 year of therapy with teriparatide his DXA measured lumbar spine BMD significantly improved (9.8% increment) without any signs of a new fracture.

Conclusions
The osteoporosis in BTM has a complex mechanism; both increased bone resorption and decreased formation being involved. Probably the extent of contribution of the two mechanisms varies in each patient. Although the bisphosphonates are the most used treatment for osteoporosis in BTM, our case report suggests that, at least in some patients, decreased bone formation is the predominant mechanism and teriparatidum could be the most appropriate therapy.

Disclosure
This paper is partly supported by the Sectoral Operational Programme Human Resources Development (SOPHRD), financed by the European Social Fund and the Romanian Government under the contract number POSDRU 141531.
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EP244
Quick PTH improves the cure rate of minimally invasive surgery in patients with primary hyperparathyroidism and preoperative localized parathyroid adenoma
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Introduction
Intraoperative quick PTH (ipPTH) monitoring is important in the treatment of primary hyperparathyroidism (pPTH), allowing, together with preoperative localisation, the switch from routine bilateral neck exploration to limited gland excision.

Aims
We checked the advantage of ipPTH for improving the cure rate of patients operated for pPTH by using minimally invasive surgery (MIS).

Materials and methods
Retrospective study comparing two groups of patients with pPTH caused by isolated sporadic parathyroid adenomas localised before surgery with sesta-MIBI scintigraphy and ultrasound. All patients were operated by MIS. Adenoma excision was histologically confirmed. The 40 patients from the first group (control, C) were operated without measuring ipPTH, whereas ipPTH and serum calcium were assessed in the second group (ipPTH) of 13 patients 5 min after the excision of the adenoma and before wound suture. When ipPTH dropped <50% the pre-excision value, MIS was converted to open neck surgery.

Results
Six out of the 40 patients from the C group (15%) had persistent hypercalcemia and elevated PTH at 24 h, 3 and 6 months after surgery, needing reintervention. Eleven out of the 13 patients from the ipPTH group had an important drop of ipPTH after adenoma excision, whereas two of them (15.4%) persisted having high ipPTH levels. Conversion to open neck surgery allowed localising a preoperatively undetected supplementary parathyroid adenoma in both cases. Excision of the second adenoma allowed PTH normalization and cure in only one surgical intervention, thereby increasing success rate to 100% in the ipPTH group (P<0.05).

Conclusion
The addition of an ipPTH assay to MIS provides a quick and reliable intraoperative confirmation of accurate adenoma removal. ipPTH is able to distinguish between single and multiple gland disease. Persistence of high ipPTH indicates conversion of single and multiple gland disease. Hypogonadotropic hypogonadism, secondary diabetes mellitus (2008), and hypothroidism (2009). For his endocrine complications he received substitutive treatment with testosterone undecanoate, calcium, vitamin D and insulin. In January 2009 he was diagnosed with severe osteoporosis with multiple vertebral fractures, he had vertebroplasty performed at T11 and T12; alendronate treatment was initiated until November 2013 when a new vertebral fracture occurred at L5. In this context, the alendronate treatment was considered suboptimal/ineffective; therefore, therapy with ipPTH was initiated. After 1 year of therapy with teriparatide his DXA measured lumbar spine BMD significantly improved (9.8% increment) without any signs of a new fracture.

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The osteoporosis in BTM has a complex mechanism; both increased bone resorption and decreased formation being involved. Probably the extent of contribution of the two mechanisms varies in each patient. Although the bisphosphonates are the most used treatment for osteoporosis in BTM, our case report suggests that, at least in some patients, decreased bone formation is the predominant mechanism and teriparatidum could be the most appropriate therapy.

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Six out of the 40 patients from the C group (15%) had persistent hypercalcemia and elevated PTH at 24 h, 3 and 6 months after surgery, needing reintervention. Eleven out of the 13 patients from the ipPTH group had an important drop of ipPTH after adenoma excision, whereas two of them (15.4%) persisted having high ipPTH levels. Conversion to open neck surgery allowed localising a preoperatively undetected supplementary parathyroid adenoma in both cases. Excision of the second adenoma allowed PTH normalization and cure in only one surgical intervention, thereby increasing success rate to 100% in the ipPTH group (P<0.05).

Conclusion
The addition of an ipPTH assay to MIS provides a quick and reliable intraoperative confirmation of accurate adenoma removal. ipPTH is able to distinguish between single and multiple gland disease. Persistence of high ipPTH indicates conversion to bilateral neck exploration, thereby increasing cure rate in the same intervention.

Disclosure
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EP245

A rare cause of increased bone mineral density in adulthood: autosomal dominant osteoporosis

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Introduction and aim

Osteoporosis is a rare genetic disorder of reduced osteoclastic bone resorption. Defective bone remodelling induces skeletal sclerosis and abnormally dense but brittle bones. We present here a case of autosomal dominant osteoporosis type II as a cause of high bone mineral density (BMD).

Case report

A 52-years-old woman with a complaint of bone pain and headache referred to our clinic for evaluation of high BMD. Her medical history and physical examination were unremarkable. Increased BMD in DXA scanning affecting both spine and hip was classified as generalised and acquired causes were evaluated initially. Serum fluoride concentration, renal and liver function tests, IGF-1 level, hepatitis C serology were all normal excluding fluorosis, renal osteodystrophy, acromegaly, hepatitis C associated osteosclerosis. There was no spondylomalgia or hematologic abnormality for miyelofibrosis. Serum tryptase level was normal excluding mastocytosis. She denied any usage of ostrogen implants. Excluding the acquired causes, the specific features suggesting monogenic disorders such as osteoporosis or sclerosing bone dysplasias were investigated. Rugger-jersey spine due to vertebral end plate thickening, bone within bone in pelvis and transverse sclerotic bands within distal femur, the classic signs of osteoporosis, were recognized at plain radiographs. She denied any history of fracture and also, whole body radiographic survey showed no pathological fractures. Her serum acid phosphatase was high. She was diagnosed as adult type osteoporosis type II. Complication screening revealed only mild decrease in high-pitched voice in audiology.

Conclusion

Autosomal dominant osteoporosis exhibits a heterogeneous trait with milder symptoms, often diagnosed at later adolescence or adulthood. Two distinct types (type I and II) have been described on the basis of radiographic, biochemical and clinical features. Type II disease appears to increase the risk of fracture. The disease requires no treatment although the complications may require intervention.

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EP246

Hypocalcaemia due to 22q11.2 deletion syndrome diagnosed in adulthood

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Introduction

Hypocalcaemia is present in half of the patients with 22q11.2 deletion during childhood. Case report

A 56-year-old man was evaluated for symptomatic hypocalcaemia after undergoing a left nephrectomy because of renal tumour. He had paraparesis around his mouth and hands and Trousseau’s sign. His past medical history included high blood pressure, type 2 diabetes, dyslipidaemia and chronic obstructive pulmonary disease. He mentioned a hypocalcaemia episode 10 years ago, frequent bronchitis at childhood and learning difficulties. Blood tests showed hypocalcaemia of 6.2 mg/dl (NV: 8.4–10.2) hyperphosphataemia of 7.08 mg/dl, hyperparathyroidism of 4.8 mg/dl (2.3–4.7) and normal magnesium. Parathyroid hormone (PTH) was 29.7 g/l, (35–50 g/l), corrected calcium of 7.08 mg/dl, hyperphosphataemia of 2.3–4.7) and 1.25-dihydroxy vitamin D 20.1 pg/ml (26.1–95). Thyroid function was normal. The electrocardiogram showed no prolonged QT interval. Endovenous and oral calcium and calcitriol were initiated, with normalization of calcium levels. Based on hypocalcaemia secondary to primary hypoparathyroidism anti-parathyroid antibodies and anti-calcium sensor receptor antibodies were requested. Due to childhood medical history and dysmorphic phenotype (hooded eyelid, bulbous nasal tip) a genetic test of 22q11.2 deletion was made. Anti-parathyroid antibodies were negative, anti-calcium sensor receptor antibodies finally were not made and the genetic test confirmed the diagnosis, so more tests were made in the outpatient clinic. Treatment at discharge was oral calcium and calcitriol. Echocardiography was normal. Densitometry revealed no bone mass loss. Immunologic studies showed a mild disturbance of cellular immunity. He received genetic advice of affected offspring.

Conclusions

It is important to classify hypocalcaemia diagnosed at any age, and especially hypocalcaemia due to genetic syndromes, as in our case, due to the 50% risk of an affected offspring.

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EP247

Clinical and biochemical response to denosumab in a young adult patient with craniofacial fibrous dysplasia

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We report on the clinical and biochemical outcomes in a 20-year-old male suffering from active craniofacial monostotic fibrous dysplasia (MFD) treated with the RANK-L inhibitor, Denosumab, following unsatisfactory responses to prior long-term bisphosphonates therapy. The patient had been treated over 9 years with pamidronate (cumulative dose of 81 mg), but experienced only mild reductions in pain scores. Following initiation of Denosumab 60 mg subcutaneously, bone pain and bone turnover markers (osteocalcin, total and bone alkaline phosphatase and β-crocollaps) were monitored over a period of 14 months. Following the first administration, the patient demonstrated a promptly and pronounced clinical and biochemical response: within few hours the patient reported pain disappearance and after 4 weeks bone turnover markers fell to levels within the normal range. Three months after initiation of Denosumab the patient reported an acute pain reactivation that required a second administration. As previously, after few hours the pain disappeared. Later Denosumab was administered according to pain reappearance and the injections were always followed by complete pain relief. However, a gradual shortening of the pain-free interval between administrations was observed, ranging from 90 days after the first one to 75 days after the fifth one. Treatment with Denosumab was always well tolerated. The monitoring of bone turnover showed that all markers stayed in the lower half of the normal range, even at the moment of pain reappearance, suggesting that the effect of Denosumab on pain depends on mechanisms other than bone resorption suppression.

In conclusion, Denosumab appears to be effective in reducing bone turnover and bone pain in adult patients with active MFD and could represent a good alternative to bisphosphonates, allowing to avoid elevate cumulative doses of these agents. Further studies are required to clarify the efficacy, safety and mechanisms of long-term therapeutic RANK-L inhibition in MFD.

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EP248

Hypophosphataemic rickets: two unrelated Mexican female cases and review of the literature

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Introduction

Hypophosphatemic rickets (HR) is a rare genetic disorder characterized by poor growth, short desproportionate stature and lower limb anomalies.

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Clinical manifestations usually appear before 1 year of age, this entity is characterised by osseus hypomineralisation, secondary to the increased expression of phosphatonin, especially FGF23, which acts in the sodium and phosphate co-transporters of the proximal convoluted tubule, inducing phosphaturia. HR exhibits AD, AR or X-linked inheritance patterns.

Objective
We present two unrelated HR case reports, with clinical radiological and laboratory studies of Hypophosphataemic Rickets with osseous complications and adverse medical events.

Case reports
Case 1: 7.6-year-old girl, physical examination showed height 113 cm, weight 24 kg, arm span 116 cm, OFC 48 cm, with disproportional short stature, genu varum, gait difficulties, asymmetric thorax; actually presenting normocalcaemic, normophosphataemia, phosphaturia, calcitriol deficiency and secondary hyperparathyroidism.

Case 2: 15-year-old girl at physical examination showed height 141 cm, weight 76 kg, with surgical antecedents, the first one in order to correct bilateral tibia deformity at age 3, and genu varum correction surgery at age 5; actually presents recidivant genu varo, normocalcaemic, hypophosphataemia, and phosphaturia.

Discussion
Hypophosphataemic rickets should be suspected in any child with disproportional short stature, developmental delay and short, malformed legs. Only one-third are due to nutritional deficit, clinical cases presented meet clinical criteria and radiological rickets. In case 1 presents normocalcaemic, normophosphataemia indicating good control in the treatment. The case 2 has normocalcaemia, hypophosphatemia and vitamin D insufficiency, renal presenting microcrystallitis and secondary hyperparathyroidism, which suggests a more aggressive disease character.

Conclusions
Due to functional complications in HR, early diagnosis and treatment is necessary, based in growth curves as well as serum values of phosphorus, calcitriol, alkaline phosphatase, and others, in order to offer an optimal medical care and prevent secondary osseous deformities.

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EP249
Analytical evaluation of a new fully automated immunoassay for the quantification of 1,25-dihydroxvitamin D
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Background
Quantification of 1,25-dihydroxyvitamin D (1,25(OH)2D) remains challenging because of low circulating concentrations and potent cross-reactivities with structurally similar metabolites. Most frequent assays for 1,25(OH)2D testing are still based on RIA format with preliminary extraction. The analytical performances and the turnaround time of analysis (TAT) for these assays are limited. Several novel assays for 1,25(OH)2D testing are emerging. The aim of our study was therefore to evaluate the analytical performances of a recently developed automated immunoassay for the measurement of 1,25(OH)2D.

Methods
We evaluated the performances of the LIAISON XL 1,25(OH)2D assay (DiaSorin), a fully automated immunoassay that uses a recombinant fusion protein for capturing 1,25(OH)2D. The limit of detection and the within- and between-run imprecision were determined. Method comparison was performed with our routine RIA method and with a reference Liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.

Results
The limit of detection was <5 pg/ml. The within-run coefficients of variation (CV) were 2.6 and 4.4% for 1,25(OH)2D concentrations of 6.7 and 19.7 pg/ml and the between-run CVs were 9.3 and 13.1% for concentrations of 25.4 and 101.1 pg/ml. The automated 1,25(OH)2D assay was significantly correlated to RIA ($r=0.74$; $P<0.0001$) and LC-MS/MS ($r=0.9975$; $P<0.0001$). The comparison of the automated assay and RIA revealed through Passing-Bablok regression analysis a slope of 0.86 and an intercept of 14.12. The mean bias observed on the Bland-Altman plot was $-2.8$ pg/ml. The comparison of automated assay and LC-MS/MS revealed through Passing-Bablok regression analysis a slope of 1.07 and an intercept of $-1.87$. The mean bias observed on the Bland-Altman plot was $-8.2$ pg/ml.

Conclusion
The LIAISON XL 1,25(OH)2D automated assay demonstrated superior analytical performances in comparison to RIA assay and a clear improvement of TAT.

EP250
High offset point for normocalcaemic secondary hyperparathyroidism due to vitamin D deficiency
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Introduction
Vitamin D deficiency occurs more frequently in patients with primary hyperparathyroidism compared to general population, and is usually associated with an aggravated form of the disease. Current guidelines recommend measurement of vitamin D level in all patients with primary hyperparathyroidism, and their repletion if the levels are <50 nmol/l.

Case report
We present a 56 years old Caucasian lady who underwent right parathyroidectomy & thyroid lobectomy for right parathyroid carcinoma in 1998. Her initial serum parathyroid level was 48.2 pmol/l (1.1-6.4). Postoperatively, her parathyroid level improved to 7.5 pmol/l but never came back to normal. She was followed up in endocrine clinic for persistent normocalcaemic hyperparathyroidism with no evidence of recurrent parathyroid cancer. In January 2010 her parathyroid level was 7.8 pmol/l with concomitant vitamin D level being 90-76 pmol/l (<50 pmol/l). She was started on ergocalciferol 400 IU twice daily. After 6 months, her parathyroid levels were 4.3 pmol/l which suggested secondary hyperparathyroidism due to relative vitamin D deficiency. In March 2012, despite being on vitamin D supplementation, her parathyroid levels were elevated at 6.6 pmol/l with vitamin D level being 86 nmol/l. She was advised to continue with same dose of vitamin D supplement. In March 2014, her parathyroid level increased further to 8.6 nmol/l with her being vitamin D replete at 107 nmol/l. This time it was decided to increase the dose of vitamin D to 2000 IU/day. After 6 months of treatment with increased dose of vitamin D, her parathyroid level normalized to 4.6 pmol/l with vitamin D levels of 152 nmol/l. She was normocalcaemic during all this time.

Discussion
In this patient, her parathyroid levels normalised after achieving a vitamin D level, which was higher than usually recommended level. In selected patients, we may need to aim for a higher vitamin D level before seeing an improvement in parathyroid levels.

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EP251
Low bone mass in Sheehan’s syndrome: prevalence and management
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Introduction
Hypopituitarism is a known cause of bone mineral loss. Our study aimed to evaluate the frequency of osteopenia and osteoporosis in patients with Sheehan’s syndrome and to evaluate its management.

Subjects and methods
It is a retrospective longitudinal study concerning 60 cases of Sheehan’s syndrome that have had a bone mineral density measurement. The parameters of osteodensitometry, the received treatment and the follow up data were collected. The baseline parameters of osteodensitometry were compared to those of 60 age-, height- and weight- matched healthy control women.

Results
The mean age at osteodensitometry measurement was 49.4 ± 9.9 years (range 25–76 years). Osteopenia was present in 25 patients (41.7%) and osteoporosis in 25–76 years). Osteopenia was present in 25 patients (41.7%) and osteoporosis in 23 (38.3%). Bone mineral density was significantly lower than in the control group ($P<0.001$). The odds-ratio of osteopenia-osteoporosis was 6.3. Low bone mineral mass concerned more frequently lumbar spine ($P<0.05$). Bone fracture was reported by three patients (5%). Only six of the osteoporotic patients were treated with bisphosphonates. Osteodensitometry was controlled in 15 cases after a mean duration of 6 years and showed an improvement in four cases.

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Conclusion
Low bone mineral mass was very frequent in patients with Sheehan’s syndrome. Treatment was insufficient.

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EP252
Comparison of the pre-operative and post-operative haemogram parameters of the patients with primary hyperparathyroidism
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Anaemia prevalence is reported between 5 and 31.8% in patients with PHPT. Anaemia in PHPT shows correlations with serum calcium, PTH, alkaline phosphatase levels, severity of the bone disease and PHPT duration. In this study we compared pre-operative and post-operative haemogram parameters of patients with PHPT who received a parathyroidectomy at our department. We determined the prevalence of pre-operative anaemia, thrombocytopenia, neutropenia and observed if any of these parameters were recovered after the surgery. We excluded patients with systemic diseases which may interfere with cytopenia. Likewise, we determined pre-operative and post-operative variations of some parameters such as RDW, MPV, neutrophil/lymphocyte rates, that are often disregarded in haemogram reports but related to chronic inflammation. Out of 157 patients with PHPT, 127 (80.9%) were women and 30 (19.1%) were men. There was no significant difference in terms of prevalence of cytopenia before and after the surgery for PHPT. Correlation analysis did not reveal any significant differences between studied parameters except that there was a moderate-weak relation between PTH level and neutrophil/lymphocyte rate. Mean RDW was high in patients with PHPT before the surgery, however it did not improve after the operation significantly. There are no studies in the literature evaluating RDW, MPV values and neutrophil/lymphocyte rates that are related to primary hyperparathyroidism (or secondary, tertiary hyperparathyroidism). Our study has the feature of being the first study in this field, more significant data is expected to be obtained as the number of included patients increase.

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EP253
TSH and free-T3 correlate negatively and independently with bone mineral density in adults with subclinical hypothyroidism
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The role of the thyroid receptor (TSHR) in bone is unclear. TSHR-deficient mice have low bone mineral density (BMD) and focal osteosclerosis despite normal thyroid hormones (suggesting TSHR function, in bone, is important). Subclinical hypothyroidism (SH) has various aetologies including thyroid autoimmunity (TA) and inactivating TSHR mutations (TSHR-M). In TSHR-deficiency & TSH-M elevated TSH compensates for reduced TSHR function, whereas in TA it compensates for reduced thyroid synthetic responsiveness (inflammation mediated). We hypothesised differential bone effects in SH relating to these causes.

Aims
i) To establish whether free-T4, free-T3 or TSH are associated with BMD and bone turnover (BT) in SH. ii) To explore whether SH aetiology influences BMD and BT.

Methods
208 adults with primary untreated SH (TSH ≥ 2.5 mU/l) and free of known bone disease were recruited. A medical/lifestyle history, anthropometric data and blood samples were collected (free-T4, free-T3, TSH, anti-TPO antibodies, BT markers (CTX, P1NP)). Mutational screening of the entire TSH coding region was undertaken by dHPLC and confirmed by direct sequencing. A DXA bone scan (lumbar spine (LS) and hip) generated Z-scores (relative to age/sex-matched normals (BMD-Z)) which were evaluated alongside thyroid parameters in stepwise multivariate regression analyses.

Results
50% of the cohort were TPO+ and 6% had TSHR-Ms. After adjustment for potential confounders, TSH associated negatively with BMD-Z at the LS (R = −1.7, P < 0.001) whereas free-T3, associated negatively with BMD-Z at both sites (hip: R = −0.35, P = 0.005; LS: R = −0.5, P = 0.002) and free-T4 showed no independent associations. Stratification by SH aetiology showed no influence of TSHR-M on BMD-Z (despite lower free-T4 relative to TSH (R = −0.34, P = 0.01)) but TPO− associated negatively with BMD-Z at the LS (R = −0.65, P < 0.001). Male gender associated negatively with BMD-Z at all sites (R = −0.8, P = 0.001). BT markers did not associate with thyroid function or BMD.

Conclusions
In adults with SH, BMD is associated negatively with free-T3, TSH, male gender and TPO antibody positivity.

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EP254
Vitamin D deficiency in patients with autoimmune thyroiditis
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There is increasing interest in the role of vitamin D deficiency in a number of chronic health problems including autoimmune diseases. The aetiology and pathogenesis of most autoimmune disorders remain obscure and a number of factors have been implicated in their pathogenesis, one of the most recent agents found to be associated with autoimmunity is vitamin 25(OH)D. The aim of the study was to assess total vitamin 25(OH)D status in patients with autoimmune thyroiditis with subclinical and overt hyperthyroidism.

Methods and materials
70 patients (54 females and 16 males) and 20 apparently healthy individuals with matched age and sex were underwent a detailed clinical examination, thyroid function tests (TSH, fT4, fT3, thyroid peroxidase antibodies) and serum total vitamin 25(OH)D.

Results
The patient group with autoimmune thyroiditis was classified according to the level of TSH into subclinical and overt hypothyroid groups. Levels of serum TSH were significantly increased in subclinical (6.80 ± 1.84 IU/ml) and hypothyroid (10.24 ± 2.09 IU/ml) groups as compared to control group (2.16 ± 0.39 IU/ml) (P < 0.05). The thyroid peroxidase antibodies level was 312.83 ± 7.19 IU/ml in subclinical hypothyroid group and was 529.31 ± 9.62 IU/ml in the hypothyroid group. The levels of serum total 25(OH)D were significantly decreased in subclinical (18.8 ± 1.2 nmol/l) and overt hypothyroid groups (21.9 ± 1.1 nmol/l) as compared to control group (27.1 ± 1.2 nmol/l), (P < 0.05). A highly significant negative correlation was found between serum TSH, thyroid peroxidase antibodies and total 25(OH)D levels (P < 0.001). Also highly significant positive correlation was found between the levels of serum total 25(OH)D and serum fT3 (P < 0.001). There was significant positive correlation between TSH and thyroid peroxidase antibodies levels (P < 0.05).

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EP255
PTH 1–34 replacement therapy in post-surgical hypoparathyroidism: preliminary results from the 6-month follow up study
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Hypoparathyroidism is characterised by parathyroid hormone (PTH) levels inadequate to maintain plasma calcium concentration within the normal range. Even if the conventional treatment with calcium supplements and active vitamin D analogues is usually able to maintain normocalcemia, episodic low plasma calcium, neuromuscular complaints, renal disease and gastric discomfort are not infrequent. 29 patients with post-surgical hypoparathyroidism were started on PTH 1–34 therapy, because of persistent low plasma calcium, related to low calcium intake due to calcium intolerance and decreased quality of life (QoL).

The still ongoing protocol includes periodic visits with biochemical exams,
EP256
Vitamin D is essential for the musculoskeletal health, its effect being independent of age, menopause or PTH level: our study aims to find the threshold of 25OH-D, suggestive for osteoporosis
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We evaluated 341 postmenopausal women, aged 29–84 years (mean age 58.18 ± 9.01) and referred to the Center for Osteoporosis starting December 2013. Secondary causes of osteoporosis/bone loss and patients under antosteoporotic medication or under vitamin D substitution were excluded from the study. All patients performed DXA measurement (Dexxum T, Osteosys, Inc., South Korea) (same expert). FRAX and 25 HO vitamin D levels were determined. We defined vitamin D deficiency as levels below 10 ng/ml and insufficiency as levels below 30 ng/ml. The mean 25 HO vitamin D value in the investigated group was 23.69 ± 11.40 ng/ml (4.1–71.3 ng/ml). Vitamin D insufficiency was present in 65.39% and deficiency in 9.38% of the cases. The level of deficiency/insufficiency increased with age, but was described even in young woman (below 40). When we analyzed the DXA results, the hip and spine density turned out to be lower in the presence of vitamin D insufficiency. Using the ROC curve and Youden index, we observed that a 25 HO vitamin D level lower than 21.80 ng/ml is highly predictive for lumbar and femoral neck demineralisation.

Conclusion
Evaluation of vitamin D status is important in the assessment of bone health in postmenopausal women, decreased levels of vitamin D being associated with increased prevalence of bone demineralisation.

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EP257
Diabetes mellitus type 1
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Materials and methods
A survey was 95 people (45 people with diabetes mellitus type 1, 50 people with diabetes mellitus type 2). The age of examined patients 39.12 ± 3.8. The disease duration ranged from 6 to 20 years. Level of biochemical indicators – normal limits. Condition of mineral density of a bone tissue it was estimated by method of a dual-energy X-ray absorptiometry (DEXA). The analysis of DEXA researches showed that change of mineral density of a bone tissue at patients with diabetes of 1 type meets – 26 (57.7%), osteoporosis at 18 people (40%), osteopenia at eight people (17.7%); norm – at 19 patients (42.3%). DEXA analysis of studies in patients with type 2 diabetes showed that 21 (42.6%) patients occurs change in bone mineral density in 8 (16%) patients – osteoporosis, 13 (26%) – diabetic osteopenia; the norm in 29 (58%). Our analysis showed that for patients with diabetes mellitus type 1 the most characteristic changes of DEXA parameters in three standard areas of study. While for patients with diabetes mellitus type 2 is characterized by changes in mineral density of bone tissue in two standard zones of the study. As well as that of patients with diabetes mellitus types 1 and 2 changes in mineral density of bone tissue previously only detected in the lumbar spine. In patients with diabetes mellitus types 1 and 2 was positive correlation between the duration of diabetes, diabetes compensation and bone mineral density (P<0.05).

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EP258
Primary hyperparathyroidism with negative pre-operative imaging: a review of current and emerging localisation modalities
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Introduction
Primary hyperparathyroidism (PHPT) is usually caused by a single hyperfunctioning parathyroid adenoma. Preoperative localization studies allow for minimally invasive surgical removal. We present a case of PHPT caused by a solitary adenoma that could not be localised pre-operatively and review existing and emerging localisation modalities.

Case report
A 65-year-old Chinese lady admitted for neck fracture was found to have hypercalcaemia of 2.82 mmol/l (RI: 2.15–2.58 mmol/l) and PTH level of 16.2 pmol/l (RI: 0.8–6.8 pmol/l). History was unremarkable for renal impairment, drug related causes or malignancy. Her calcium/creatinine clearance ratio of 2.12% was suggestive of PHPT. Ultrasonography did not localize any hypervascular ovoid structures but showed multiple thyroid nodules. Fine needle aspiration cytology (FNAC) of the thyroid nodules was negative for malignancy. Dual tracer parathyroid scintigraphy did not reveal any sestamibi-avid or enlarged parathyroid lesion. A total thyrocideotomy and exploratory parathyroidec- tomy subsequently revealed a right parathyroid adenoma embedded within the thyroid tissue.

Discussion
PHPT is accounted for by a solitary adenoma in 85–90% of all cases. Preoperative localization techniques allows for minimally invasive surgery which reduces morbidity. Non-invasive modalities include ultrasonography, parathyroid scintigraphy, sestamibi-single photon emission computed tomography (SPECT), 4-dimensional CT, positron emission tomography and MRI, with scintigraphy being the most sensitive (scintigraphy 54–96%, 4D-CT 88%, SPECT 79%, ultrasonography 76%, MRI 43–71%). The sensitivity of scintigraphy is decreased in four-gland hyperplasia, double adenomas or concomitant thyroid disease. The results of scintigraphy can be enhanced by combination with SPECT or using dual tracer subtraction scans. Invasive techniques such as venous PTH sampling and selective arteriography are reserved for patients with recurrent or persistent hyperparathyroidism.

Conclusion
The pre-operative localisation of a solitary adenoma in PHPT remains a challenge despite new, emerging techniques.

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EP259
Rapid and profound decrease in resorption markers preceded early and profound increase in BMD after successful surgery in osteitis fibrosa cystica
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Introduction
Successful parathyroid surgery in patients with OFC leads to early and marked improvements in BMD but data on very early changes in bone markers are missing.

Case report
A 20-year-old girl was hospitalised because of severe bone pains and multiple pathological fractures (left humerus and left proximal femur) after minimal trauma. She had lost weight, was amenorhoeic for the last 12 months and was bleeding from brown tumours in her mouth. She was unable to walk and was
complaining for general fatigue, anorexia, polyuria and polydipsia. Skeletal X-rays revealed multiple osteolytic lesions throughout the entire skeleton, brown tumours in the mandible and OCP change of the left shoulder. Serum calcium and PTH were of 14.7 mg/dl and 1243 pg/ml, respectively; alkaline phosphatase activity was 1372 U/l. After hydration with i.v. sodium chloride, the patient was given i.v. pamidronate (60 mg) and serum Ca fell to 12.4 after 2 days. The patient underwent parathyroid surgery and a right superior parathyroid adenoma (2.2 g) was removed. She was treated with oral calcium carbonate (2.4 g daily) and cholecalciferol 2000 U/daily. A marked reduction in BMD at LS (0.594 g/cm²), FN (0.530 g/cm²) and total body (0.680 g/cm²) was seen by DXA, with T-scores in the markedly osteoporotic range (−4.9 and −3.9 s.d., respectively). After 9 months there were increases of 23.7, 39.6 and 31.2%, respectively; after 2 years of 44.1% (LS) and 64% (FN). In three other similar cases (OPC on X-ray) serum CTX decreased after 1 month by three to six times, while OC increased in one patient by 1.2 times and decreased in the other two by 90 and 53%, respectively. After 1 year CTX and OC were normal in the two patients with available data.

Conclusion
The cases show an unexpected rapid and profound decrease in resorption just 1 month after surgery while formation decreased at a much slower pace, changes that preceded the marked increase in BMD, especially at the cortical sites.

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EP260
Primary hyperparathyroidism in pregnancy: a case series
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Introduction
Primary hyperparathyroidism (PHP) in pregnancy is very rare condition and the true incidence of PHP in pregnancy is not well known. PHP is associated with significant maternal and foetal morbidity and mortality. PHP is diagnosed based upon levels of blood calcium and parathyroid hormone (PTH) in normal renal function status. However diagnosis of PTH can be difficult, the physiological changes of pregnancy in calcium homeostasis such as maternal blood volume expansion, hypalbuminaemia and increased glomerular filtration rate contribute to the difficulty of PHP diagnosis during pregnancy.

Cases
We present four case reports about patients, having PHP in pregnancy. Three of patients, not to be controlled biochemically, denied the parathyroidectomy operation although they are informed about the details of their disease. They are followed up with medical therapy. The first one had no maternal or foetal complications, the second one acquired nephrolithiasis crisis in the last trimester and the third one gave a birth prematurely born baby who succumbed to tetany. The fourth patient who underwent parathyroidectomy operation in the second trimester had no maternal or foetal complications.

Conclusion
PHP in pregnancy is a preventable cause of foetal and maternal morbidity and mortality. Suspecting PHP during the pregnancy period and an early diagnosis can provide maternal and foetal well-being. During pregnancy, surgery should be avoided in the first and third trimester and conservative management should be preferred instead. Current evidence supports parathyroidectomy as the main treatment in the second trimester of pregnancy.

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EP261
Comparative effectiveness of bisphosphonates and parathyroidectomy in osteoporosis related to primary hyperparathyroidism
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Introduction
The use of Bisphosphonates could be a treatment option of osteoporosis secondary to primary hyperparathyroidism (OPHP) in patients not eligible or that refuse/reject surgery.

Methods/design
We analysed data of 46 patients diagnosed of OPHP. Fourteen underwent surgery and 32 were treated with bisphosphonates at standard dose. Densitometric parameters and of calcium-phosphorus metabolism were analyzed before and after 1 and 2 years of treatment. The analysis was performed with SPSS-20.

Results
There were not differences in age, BMI, menopause age, years since menopause, alcohol consumption, diagnosis of previous low-trauma fracture, calcium intake, create clearance, serum PTH, urinary calcium, serum alkaline phosphatase, urinary D-pyridinoline, vitamin D; neither in the mineral density (MD) of lumbar spine, femoral neck or total hip at baseline between groups. Smoking was more frequent and serum calcium lower in the bisphosphonate group (BG) (P<0.05). Serum calcium and PTH decreased after 1 and 2 years of treatment within surgery group (SG) (P<0.01) but remained stable in the BG. Urinary calcium decreased in the SG, urine D-pyridinoline decreased in the BG and Serum alkaline phosphatase decreased in both groups after 1 and 2 years. There were no differences between groups. The lumbar spine MD increased after 1 year (0.754±0.121 vs 0.785±0.132; P<0.01) and 2 years (0.754±0.121 vs 0.791±0.107; P<0.01) in the BG, and only after 2 years (0.749±0.144 vs 0.794±0.189; P<0.05) in the SG. Femoral neck MD increased after 1 year (0.622±0.091 vs 0.640±0.093; P<0.01) but remained stable after 2 years in the BG. It also remained stable in the SG and in total hip MD in both groups. No differences were found between groups in MD in any location.

Conclusions
Bisphosphonates treatment could be as effective as parathyroidectomy in the treatment of OPHP.

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EP262
Investigating the bone metabolic parameters and serum 25-hydroxyvitamin D levels in male patients with asymptomatic hyperuricemia
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Introduction
Over the past few years the clinical relevance of serum uric acid level has changed. The elevated serum uric acid level not only impairs the joints and the kidney function but it is also linked with an increased risk of cardiovascular diseases. The aim of our study was to examine how bones are affected (change of bone mineral density (BMD), bone metabolism parameters, serum 25-hydroxyvitamin D levels and frequency of fractures) by elevated serum uric acid level.

Materials and methods
We investigated a total of 136 patients divided into two groups according to serum uric acid level: 68 male patients with (age: 54.9±1.8 years) and 68 male patients without (age: 55.2±1.9 years) hyperuricemia. In all cases hyperuricemia (ser level > 428 µmol/l) was asymptomatic. BMD was measured by dual-energy X-ray absorptiometry (DEXA), for bone markers such as: parathyroid hormone (PTH), β-CrossLaps, 25-(OH) vitamin D3 and osteocalcin (OC) electrochemiluminescence immunoassay was used and routine labor parameters were measured. Medical history including prevalence of bone fractures was also recorded. Statistical analysis was performed by ANOVA, with post-hoc Bonferroni correction (Satistica software 9.0).

Results
In patients with asymptomatic hyperuricemia lumbar spine (L2-4) BMD (T-score: -2.53±0.20 vs -1.91±0.20, P<0.05) and left femoral neck BMD (T-score: -2.45±0.16 vs -1.98±0.15, P<0.05) were lower than in patients without hyperuricemia. Serum 25-(OH) vitamin D3 levels were also lower in the hyperuricemic group (48.4±15.1 nmol/l vs 55.8±16.7 nmol/l, P<0.05). Bone fracture had occurred in 17 of 68 hyperuricemic patients, while in the non-hyperuricemic group only seven fractures were recorded.

Conclusions
The in-time recognition and treatment of elevated serum uric acid level could positively influence the bone metabolism and be part of fracture prevention.

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**EP263**

**Clinical outcome of patients with parathyroid gland carcinoma – single centre experience**  
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**Aim**  
To determine clinical predictors of parathyroid gland carcinoma recurrence.

**Methods**  
We evaluated outcome of eight patients with primary hyperparathyroidism due to parathyroid carcinoma who were followed at University Hospital Centre Zagreb in period from 2004 to 2014. The median follow-up was 6 (range 2–14.5) years. Six patients (three male, three female; median age 57.5 (42–71) years) experienced long-term remission after the surgery whereas two patients had unfavourable course of the disease. In patients with remission hypercalcaemia was known in median for 4 (1–16) years before the surgery. At the time of diagnosis median PTH was 48 (24–147) pmol/l (normal value 0.2–6.7 pmol/l). All of them had renal impairment, hypertension and osteoporosis with two of them previous fractures. Following surgery hypercalcaemia rapidly developed requiring intravenous calcium replacement and prolonged hospital stay. Two female patients (age at diagnosis 31 and 32 years) had poor disease outcome. Their initial diagnosis was established on the basis of acute complication of hypercalcaemia; one of them was pregnant and her newborn had severe neonatal hypocalcaemia whereas another patient had episode of acute pancreatitis. Formerly they had no recognized comorbidities related to hypercalcaemia with the exception of osteoporosis without fractures. Their PTH values were 72 and 36 pmol/l and serum calcium concentrations 4.03 and 3.8 mmol/l respectively. Following surgery there were no clinical manifestations of hypocalcaemia and no need for intravenous calcium supplementation. Within 1 year hypercalcaemia reoccurred and metastatic disease was confirmed. In both patients multiple endocrine neoplasia was excluded and chromogranin was repeatedly negative.

**Conclusion**  
Younger age, lack of chronic consequences of hypercalcaemia and hyperparathyroidism, no signs of severe symptomatic hypocalcaemia following surgery and no need for postoperative calcium supplementation could be clinical predictors of parathyroid gland carcinoma recurrence.

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**EP264**

**Measuring BMD at forearm aids in diagnosing osteoporosis and identifies more patients for surgery in asymptomatic primary hyperparathyroidism**  
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**Introduction**  
Reduction in bone mineral density (BMD) is a common feature in primary hyperparathyroidism (PHPT), involving mostly cortical site. In the management of asymptomatic PHPT (aPHPT), guidelines indicate measuring BMD at lumbar spine, hip and forearm and surgery is recommended for patients with a T-score of −2.5 or less at one of these sites. However, BMD at forearm is not always performed.

**Aim**  
Our aim was to evaluate the impact of measuring forearm BMD in the clinical and therapeutic management of aPHPT.

**Subjects and methods**  
We retrospectively reviewed a prospective database of 116 patients with aPHPT at our institution between 1998 and 2013. The study cohort was identified by examining those patients who at the time of diagnosis had a dual X-ray absorptiometry (DXA) scan at all three sites. In all patients we measured PTH, total serum and ionized calcium, urinary calcium excretion, vitamin D and creatinine levels.

**Results**  
Out of 116 patients with aPHPT we identified 13 (group A, 11.2%) who had a T score lower than −2.5 at forearm only, of which 6 (5.2%) possessed the criteria for surgery identified on the basis of forearm BMD only. Group B were the remaining 103 patients. Group A was older than group B (71 ± 7.6 vs 62.7 ± 11.8 years, P < 0.016) while no significant difference was found in the biochemical measurements or in the BMD values at either of the other sites.

**Conclusions**  
In a series of aPHPT, in 11.2% of patients, DXA on three sites revealed osteoporosis at forearm, but not at other sites. Among these patients, half were identified for surgery based on BMD at forearm. Except for age, these patients did not show any clinical, biochemical or BMD difference from the remaining patients. Preoperative forearm DXA increases the number of patients who meet the criteria for surgery based on BMD alone.

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**EP265**

**Severe refractory hypocalcaemia associated with osteoblastic metastatic breast carcinoma**  
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**Introduction**  
Hypocalcaemia is well associated with metastatic malignancy. Hypocalcaemia is an uncommon complication of osteoblastic metastases and occurs most commonly with breast and prostate carcinoma.

**Case**  
A 46-year-old woman with metastatic breast carcinoma and osteoblastic skeletal metastases treated with denosumab presented with severe symptomatic hypocalcaemia. Serum calcium was persistently low with a nadir value of 1.45 mmol/l (2.2–2.6) and predated the use of denosumab. 25OH-cholecalciferol level was low (24.1 nmol/l). Serum PTH was inappropriately normal at 4.3 (1.3–7.3) for the prevailing level of hypocalcaemia suggesting hypoparathyroidism. Renal function and magnesium were normal.

**Management**  
Treatment with intravenous calcium gluconate was instituted during symptomatic episodes. Vitamin D deficiency was managed with high dose cholecalciferol (20 000 IU, three times a week for 12 weeks) and oral calcium equivalent to 6 g of elemental calcium was commenced. Symptomatic hypocalcaemia persisted despite progressively increasing doses of elemental calcium (final dose 9 g). In view of persistent hypocalcaemia, treatment with Bendroflumethiazide 2.5 mg/day and Alfacalcidol 1 μg/day was instituted. The dose of Alfacalcidol was incrementally increased to 8 μg/day. Normocalcaemia was achieved in 16 weeks.

**Discussion**  
Hypocalcaemia is an uncommon complication of malignancy and is caused by osteoblastic bone metastases. The putative mechanism is increased uptake of calcium by osteoblastic lesions. Hypocalcaemia in our patient was exacerbated by denosumab therapy and vitamin D deficiency. However, hypoparathyroidism in the context of severe hypocalcaemia was suggestive of impaired parathyroid reserve presumed secondary to microscopic malignant infiltration of the parathyroid glands.

**Conclusion**  
Malignancy-related hypocalcaemia occurs almost exclusively with osteoblastic bone metastases and is generally associated with secondary hyperparathyroidism. Our case highlights the fact that microscopic malignant infiltration of the parathyroid glands can occur with advanced malignancy and result in severe refractory hypocalcaemia. Supraphysiologic doses of elemental calcium and vitamin D are generally required to induce and maintain normocalcaemia.

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**EP266**

**Osteoporotic fracture risk in menopausal women with obesity**  
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**Introduction**  
Osteoporosis is a metabolic disease that is characterised by low mineral bone density (BMD) and increased risk of fractures. Weight loss reduced BMD and increased risk of hip fractures, while it reduces in a weight gain. Osteoporosis
fracture risk and BMI correlate more frequently denied in recent studies. The aim of this study was to examine relationship between BMI and BMD in a group of postmenopausal women.

Design
The study involved 100 postmenopausal women, aged 46 to 70 years (59.08 ± 6.07). BMI was determined by DXA method (dual energy X-ray absorptiometry) by Lunar Prodigy Advance Unit. BMD was measured at lumbar spine and both hips. BMI values were correlated with total T score values of the lumbar spine and both hips, as well as total T score values of spine and hip. Results have shown that BMI was normal in 18% subjects, 1st grade obesity was found in 52%, 2nd grade obesity in 23%, 3rd grade obesity in 7% of subjects.

Median BMI value was found in 28.27 and P = 0.08 vs 0.826. 1Medical Faculty, Clinic of Endocrinology, Diabetes and Metabolic Diseases, Clinical Centre of Vojvodina, University of Novi Sad, Novi Sad, Serbia; 2Medical Faculty, Emergency Center, Clinical Centre of Vojvodina, University of Novi Sad, Novi Sad, Serbia; 3Smart Line Agency, Novi Sad, Serbia.

**EP267**
Evaluation of the effect of bisphosphonate therapy of postmenopausal osteoporosis using Dolga index
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Introduction
Bisphosphonates are commonly used in the treatment of osteoporosis. The aim was to determine the effect of bisphosphonate therapy for osteoporosis on bone mineral density (BMD) depending on the Dolga index.

Materials and methods
The study included 36 postmenopausal women with osteoporosis. BMD was measured by DXA of the spine and hip before treatment and 2 years after starting bisphosphonate therapy. Parameters of bone turnover: osteocalcin and beta crosslaps were measured before treatment. On the basis of these values was calculated Dolga index. The Dolga index expresses excessive suppression of bone resorption and excessive suppression of the entire remodelling if the value obtained above 0.

Results
Average age of the respondents was 62.94 ± 8.49 years, with a mean BMI 25.60 ± 3.68 kg/m². After 2 years of therapy, a statistically significant difference in the parameters of bone remodelling and BMD (OC: 37.05 ± 6.07 ng/ml, P < 0.05; L1–4 BMD: 0.803 ± 0.010 vs 0.862 ± 0.132 g/cm², total hip: 0.793 ± 0.08 vs 0.826 ± 0.07 g/cm²; hip neck: 0.764 ± 0.08 vs 0.07 ± 0.78 g/cm²) was observed. Using Dolga index, statistically significant improvement in spine and hip BMD were obtained in the group that did not have excessive suppression of bone resorption and bone remodelling. (L1–4: 0.803 ± 0.010 vs 0.847 ± 0.009 g/cm², P < 0.05; total hip: 0.792 ± 0.007 vs 0.825 ± 0.008 g/cm², P < 0.05; hip neck: 0.780 ± 0.005 vs 0.802 ± 0.006 g/cm², P < 0.05).

Conclusions
The use of bisphosphonate therapy leads to improvements in BMD with primary effect on bone resorption affecting the overall bone remodelling. The test results demonstrate the usefulness of the application of Dolga index in choosing patients with postmenopausal osteoporosis for the application of bisphosphonate therapy in order to achieve the best therapeutic effect. Continued research is ongoing on a larger scale in order to confirm the results, make new conclusions and recommendations for the treatment of postmenopausal osteoporosis bisphosphonate therapy.

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**EP268**
Patients with new onset diabetes after liver transplantation have higher sclerostin levels that tend to decrease after an oral glucose tolerance test
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Introduction
Decreased bone formation has been proposed as a mechanism involved in the higher risk of fractures in diabetic patients. Some clinical studies have found that sclerostin (SCL, a negative regulator of bone formation) is increased in diabetic patients. However, there is no information about the relationship between SCL and new onset diabetes after transplantation (NODAT). The aim of our study is to evaluate serum SCL levels in a cohort of patients with liver transplantation (LT). Patients and methods
85 LT patients without previous diabetes mellitus were enrolled. A 75 g oral glucose tolerance test was performed (OGTT) and diagnostic ADA criteria were followed. Serum SCL was measured in fasting, 60- and 120-min samples during OGTT. MANOVA test were used to evaluate the relationship of sclerostin levels (from baseline to 120-min).

Results
48 patients (64%) showed normal glucose tolerance (NGT), 31 (36.4%) impaired glucose tolerance (IGT) and six NODAT (7.05%). Results of SCL for OTTG were (ng/ml; baseline, 60’, 120’): i) NGT: 0.70 ± 0.270/0.65 ± 0.220/0.69 ± 0.23 mg/ml; ii) IGT: 0.83 ± 0.31/0.71 ± 0.20/0.75 ± 0.20 mg/ml; iii) NODAT: 1.75 ± 1.20/1.55 ± 1.24/1.46 ± 1.11 mg/ml. SCL levels were significantly higher in NODAT patients at baseline (P < 0.001); 60’ (P < 0.001) and 120’ (P = 0.001). During OGTT, sclerostin showed a significant decrease (P = 0.01), which was more pronounced in the NODAT group, with a percent of change of: –0.32 ± 0.64.

Conclusions
Our results show that after LT basal SCL levels are higher in patients with NODAT than in patients with prediabetes or NGT. Also, we have found that during an OGTT sclerostin significantly decrease, particularly in NODAT patients. Based on our results, we suggest further studies to investigate a plausible link between higher levels of sclerostin in NODAT patients and their increased fracture risk.

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**EP269**
X-linked hypophosphatemia: an Indian kindred
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Introduction
X-linked hypophosphatemia is an extremely rare disease, so far described in only two multigenerational kindreds. In US, who later on the genetic testing were found to be interrelated. We describe X-linked congenital hypophosphatemia in a family from India.

Case report
Case 1 presented with hypocalcaemic non-febrile generalised tonic-clonic seizures at 16 months of age. Seizures controlled after hypocalcaemia correction. He was put on T. calcitriol 0.5 mg B.D. 1.5 g calcium/day. Case 2 presented with hypocalcaemic neonatal generalised tonic-clonic seizure. He was put on calcitriol 0.5 mg/day, 1 g of calcium. Both had delayed milestones and growth, developed hypophosphatemia.

<table>
<thead>
<tr>
<th>Case</th>
<th>S.citriol at diagnosis (ng/L)</th>
<th>S.phosphate at diagnosis (mmol/L)</th>
<th>T.parathyroid at diagnosis</th>
<th>iPTH at diagnosis</th>
<th>S.citriol at present (ng/L)</th>
<th>S.phosphate at present (mmol/L)</th>
<th>iPTH at present</th>
<th>Average 24 hr urinary calcium in last 6-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>19-year male</td>
<td>1.05</td>
<td>10.61</td>
<td>16</td>
<td>&lt;1</td>
<td>8.4</td>
<td>6.1</td>
<td>5.2</td>
<td>340</td>
</tr>
<tr>
<td>14-year male</td>
<td>2.3</td>
<td>0.64</td>
<td>12</td>
<td>&lt;1</td>
<td>9</td>
<td>2.2</td>
<td>3.9</td>
<td>250</td>
</tr>
<tr>
<td>19-year old</td>
<td>0.6</td>
<td>4</td>
<td>22-year-old</td>
<td>0.4</td>
<td>4.3</td>
<td>Father</td>
<td>0.9</td>
<td>3.9</td>
</tr>
</tbody>
</table>

Table 1

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EP270

A case of a mitochondrial myopathy with multiple endocrinopathy
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Introduction
Mitochondrial diseases usually occur by mutations of mitochondrial or nuclear DNA. Mitochondrial cytopathy is a disease affecting many systems including endocrine system. We present a case diagnosed as mitochondrial myopathy previously accompanying multiple endocrinological pathologies.

Case
Fifty-two years old female patient admitted in another center with a complaint of drooping of upper eyelids 25 years ago. Acetylcholine receptor antibodies were negative and her EMG was compatible with progressive external ophthalmoplia. She was diagnosed as mitochondrial myopathy by left biceps muscle biopsy. Coenzym Q 10 and l-carnitine treatments were started. She admitted to our center with numbness and spasm in her hands. Serum calcium was 6.1 mg/dl, phosphorus was 6.9 mg/dl, magnesium was 1.5 mg/dl and parathyroid hormone level was 8.9 ng/ml. There were common symmetric calcifications at basal ganglia, bilateral cerebellar hemispheres, thalamus and periventricular white matter in cranial CT. EEG was normal. Creatine kinase was 507 U/l, LDH was 435 U/l and plasma lactate level was 2.4 mmol/l. Calcium carbonate and calcitriol were administered to the patient with diagnosis of hypoparathyroidism. Thyroid autoantibodies were positive. Thyroid hormone levels were normal. Thyroid ultrasound was compatible with chronic thyroiditis. In eye examination bilateral proptosis and cataract were detected. Retina examination was normal. Her audiometry was normal. She was diagnosed as type 2 DM. 

Conclusion
Mitochondrial myopathies can be together with various endocrinological problems. Our patient had adult onset pure mitochondrial cytopathy and primary hyperparathyroidism, chronic autoimmune thyroiditis and type 2 DM were accompanying endocrinological pathologies. Associations with hyperparathyroidism, autoimmune thyroiditis, DM and GH deficiency have been reported in patients with Kearns Sayre syndrome in the literature. Also mitochondrial myopathy, encephalopathy, lactic acidosis, stroke (MELAS) and adrenal insufficiency’s association was reported. Because of probability of affecting multisytem, cases with mitochondrial myopathies should be evaluated for various endocrinological pathologies.

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EP271

Vitamin D receptor genotypes and their association with the 5-year changes in bone mineral density in Spanish postmenopausal women
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Our aims were to follow the longitudinal changes after 5-year in femoral neck (FN), femoral trochanter (FT), L2, L3, L4 and L2–L4 bone mineral density (BMD) in Spanish postmenopausal women and to study whether the polymorphism BsmI in the vitamin D receptor (VDR) may influence these results. We conducted a 5-year prospective study of BMD and its change in 174 women, aged 43–78 years. BMD was measured by densitometry. The women were members of the Caceres Reference Database for the Diagnosis of Osteoporosis (CAFOR), a population-based longitudinal study of BMD. Changes were analysed by Wilcoxon test. We also examined the effect of adjustments for dietary and anthropometric factors on these associations. After the 5-year period significant changes were observed in L3, L4, L2–L4, FN and FT (P < 0.001 in all cases). No significant changes were observed in L2 (P = 0.598). Before adjustments, in women homozygous for the b allele (genotype (bb) n = 25) no significant changes were observed (P > 0.05 in all cases). Women heterozygous (genotype (Bb) n = 73) had less FT BMD (P < 0.001), L4 (P < 0.001) and L2–L4 (P = 0.010) over time; no changes were observed over the 5-year period in Bb women in FN, L2 and L3 BMD. In women homozygous for the B allele (n = 76) significant loss in BMD was observed in FN (P = 0.010) and FT (P < 0.001) BMD as well as in L4 (P < 0.001) and L2–L4 (P = 0.012) BMD after the 5-year period. No changes were observed in L2 and L3 BMD (P > 0.05 in both cases). Upon adjustment for dietary and anthropometric factors no further statistically significant associations to BsmI polymorphism were found.

Our results reveal that to correctly address the association between bone loss and VDR polymorphism BsmI in small samples, it is necessary to consider the variations in dietary and anthropometric factors.

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EP272

Cinacalcet remains effective in primary hyperparathyroidism after 4 years of treatment
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Introduction
Cinacalcet is an oral calcimimetic indicated in treatment of primary hyperparathyroidism in patients who are unable to undergo parathyroidectomy: do not accept surgery, there is failure of previous surgery or serious comorbidity that makes surgery impossible.

Methods
Descriptive study that includes nine patients with primary hyperparathyroidism who have completed at least 48 months of treatment with cinacalcet (seven patients refusal to parathyroidectomy and two surgery not possible due to comorbidities). We recorded clinical and biochemical data at baseline and after 3, 6, 12, 24 and 48 months of treatment.

Results
Median time of treatment was 49 months. After 12 months serum calcium was significantly decreased as compared to baseline (10.12 vs 11.59 mg/dl P = 0.008) and phosphorus levels were significantly increased (2.84 vs 2.45 mg/dl P = 0.021). No significant differences were observed in PTH levels (155.45 vs 136.9 pg/ml P = 0.6). No further variation was observed after 24 and 48 months compared to 12 months follow up except for an increase in PTH to baseline levels. As compared to baseline, after 4 years of therapy, serum calcium remained significantly decreased (10.13 vs 11.59 mg/dl P = 0.008) and serum phosphorus significantly increased (2.93 vs 2.45 mg/dl P = 0.02). Normocalcemia (S-Ca < 10.2 mg/dl) was achieved in 55.7% of patients. Usually the medication was well-tolerated and no serious adverse events were observed.

Conclusion
Hypercalcemia is rapidly improved by Cinacalcet and remains stable after 48 months follow-up. Cinacalcet is an effective and safe alternative in non-surgical treatment of primary hyperparathyroidism.

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EP273

Bone mineral density evolution after parathyroidectomy in patients with primary hyperparathyroidism
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Introduction
Primary hyperparathyroidism results in increased bone resorption. The presence of osteoporosis is at present an established surgery criteria.
The aim of this study was to evaluate the changes in bone mineral density (BMD) after surgery in patients with primary hyperparathyroidism.

Material and methods

Retrospective study of 58 patients with primary hyperparathyroidism treated by parathyroidectomy from 2004 to 2012. We analysed the percent change in BMD of spine, hip and radio densitometry 12 and 36 months after surgery.

Results

Among the 58 patients enrolled, we obtained densitometry data of 26 patients after 12 months and 37 after 36 months. The average age of the patients was 61 ± 12 years and 70.7% were women. We observed an increased BMD at lumbar spine and hip 1 year after surgery (+2.3% ± 5.1, P = 0.027; +5.7% ± 6.3, P =0.000, respectively). Improvement at 36 months was also observed in both locations (+4.9% ± 7.4, P = 0.001; +8.5% ± 6.0, P = 0.000). In radio, there were no changes in BMD in any of the follow-up times, although a slight increase at 36 months (+0.96% ± 4.2, P = 0.576) was observed. Sixteen of the 58 patients (27.6%) also were treated with bisphosphonates. There were no differences in changes of BMD between these patients and those who did not received bisphosphonates.

Conclusion

Hip and spine BMD improved 1 and 2 years after surgery in patient’s with primary hyperparathyroidism. It would be interesting to evaluate the response to the longer term.

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EP274

Effect of the inhibition of a cholesterol membrane transporter on vitamin D absorption: a double-blind randomised placebo-controlled study

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Introduction

Oral supplements are important to prevent and treat vitamin D deficiency. Membrane transporters could be involved in its absorption. As vitamin D is structurally similar to cholesterol, it is possible that they share absorption mechanisms. Ezetimibe decreases cholesterol absorption, through inhibition of NPC1L1 transporter. It has been shown in vitro and in rodents that ezetimibe decreases vitamin D absorption, so the aim of this study was to evaluate the effect of ezetimibe on 25-hydroxyvitamin D [25(OH)D] levels in response to a single oral dose of vitamin D, in young persons.

Methods

This randomised, double-blind, placebo-controlled trial (ClinicalTrials.gov NCT02234544) was developed in a South Brazilian University Hospital. Fifty-one medical students were randomised to ezetimibe 10 mg/day or placebo for 5 days. On the 5th and 19th days, blood samples for 25(OH)D, PTH, calcium, and albumin were collected after overnight fast. On the 5th day, all participants received a single oral 50 000 IU cholecalciferol dose during a 15 g fat meal. 25(OH)D was measured by the immunoassay Diasorin Liaison. Measurements were compared in a general linear model adjusted for multiple comparisons by the Bonferroni test.

Results

At baseline, 25(OH)D was <30 and <20 ng/ml, respectively, in all and 82.3% of the participants. Fourteen days after a single 50 000 IU oral dose of cholecalciferol, the mean (±SE) change in 25(OH)D was of 8.75 (3.74) ng/ml in the ezetimibe group, vs 10.02 (3.84) ng/ml in the placebo group, after adjustment to baseline 25(OH)D levels and BMI (P = 0.26). Mean 25(OH)D, PTH, calcium and albumin remained similar in both groups.

Conclusions

Ezetimibe had no effect on the mean change in serum 25(OH)D after a single oral dose of cholecalciferol.

Disclosure

University hospital research incentive fund (FIPE/HCPA project 14-0378).

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EP275

Acquired FGF23 resistance: the primary of parathyroid hormone over fibroblast growth factor 23 in renal phosphorus handling

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Introduction

Fibroblast growth factor 23 (FGF23) excess is the cause of chronic hypophosphatemia in rare conditions such as X-linked hypophosphataemic rickets (XLHR) and tumour-induced osteomalacia (TIO), but animal studies indicate that the effect of FGF23 on serum phosphorus is dependent on the presence of parathyroid hormone (PTH). In this case series of rare disorders with abnormalities in renal phosphorus handling, we sought to explore the relative roles of PTH and FGF23 on renal handling of phosphorus.

Methods

We studied 16 patients with congenital hypophosphataemia (of whom two were hypoparathyroid post total parathyroidectomy), two patients with TIO, one patient with hypophosphataemic bone disease due to congenital renal tubular acidosis, and three patients with hyperparathyroidism (HP). We performed genetic mutation analysis, and we measured FGF23, PTH, renal phosphorus threshold (TmP/GFR), ionised calcium, 25-hydroxyvitamin D (25(OH)D), and a panel of bone turnover markers (BTMs). We also studied 30 patients with chronic kidney disease (CKD) who had estimated glomerular filtration (eGFR) stages 3–5.

Results

Patients with congenital hypophosphataemia and TIO had low TmP/GFR and varying degrees of FGF23 excess. The patient with hypophosphataemic and renal tubular acidosis had the lowest FGF23 and the three patients with HP had low PTH, elevated FGF23, but high TmP/GFR. The two patients with congenital hypophosphataemia and hyperparathyroidism had normal TmP/GFR despite having marked elevation in both C-terminal and intact FGF23. Both patients had CKD, but FGF23 was still about tenfold higher than expected for level of eGFR.

Conclusions

While FGF23 is a determinant of TmP/GFR in congenital and acquired disorders of dysregulated FGF23 production, the full effect of FGF23 on phosphorus is dependent on the presence of PTH secretion. FGF23 resistance is extant when PTH is absent.

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EP276

Lower levels of vitamin D as a predictor of reduced muscle strength in moderately obese postmenopausal women

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Introduction

Low concentration of serum 25-hydroxyvitamin D (25-OHvitD) have been associated with low bone loss and risk of falls in postmenopausal women. Moderate obesity is not a risk factor for osteoporosis.

Aim

The aim of this study was to investigate how vitamin D concentration correlates with muscle strength and bone density in moderately obese postmenopausal women.

Methods

We include 33 postmenopausal women, between 50 and 60 years of age, coming for the first measure of dual-energy X-ray absorptiometry (DXA). The assessed parameters were: BMI, waist circumference (WC), 25-OHvitD, bone mineral density (BMD) measured by DXA and muscle strength. Muscle strength was measured as hand grip strength (HGS) with JAMAR Hand Dynamometer. Three measures on the right or left hand were averaged to get the absolute HGS and measures on the right or left hand were averaged to get the absolute HGS and

Disclosure

None

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continuous variables and Spearman test for correlations between variables were used.

Results
The postmenopausal women were 56.4 ± 2.8 years old, menopausal duration 6.5 ± 2.7 years, with BMI 28.01 ± 3.4 kg/m² and WC 89.0 ± 8.1 cm. The mean level of 25-OHvitD was 32.5 ± 13.9 nmol/l. A significant negative correlation was observed between 25-OHvitD levels and both WC ($r_{p} = -0.65; P < 0.001$) and BMI ($r_{p} = -0.49; P < 0.003$). The average HGS of these moderately obese participants was 23.6 ± 4.2 pounds. It was significantly lower than the normative grip strength for referent range group ($t = -21.65; P < 0.001$). A significant positive correlation was observed between 25-OHvitD levels and HGS ($r_{p} = 0.45; P < 0.000$). Average BMD on lumbar spine was 0.862 and 0.668 g/cm² on total hip. There was a very weak correlation between serum 25-OHvitD and BMD at lumbar spine ($p = 0.167; P = 0.35$) and hip ($p = 0.228; P = 0.20$).

Conclusion
Decreased levels of 25-OHvitD in moderately obese postmenopausal women are associated with low muscular strength. Decreased muscular strength may increase the risk of falls and fracture in moderately obese postmenopausal women.

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**EP277**

**Evaluation of calcium and vitamin D disorders: case report of two patients**

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Introduction
Differential diagnosis of hypocalcaemia is extensive, and careful diagnostic algorithm should be performed to adequately treat hypocalcaemic disorders.

Case report
Two female patients with hypocalcaemia are presented. The first one was 49 years old, admitted to hospital due to weakness, hampered mobility and bone pain (hips, thorax). Six years ago she was hospitalized due to chronic renal failure, osteoporosis, fractures of hip and both pubic bones, but did not take any medication. Current diagnostic procedures revealed several rib fractures (X-ray), and laboratory tests showed: iron deficiency, urea and creatinine increased, high alkaline phosphatase (297 U/l), low total serum (1.8 mmol/l) and ionizing calcium (0.56 mmol/l), low urinary calcium, low serum phosphate, low vitamin D (34 mmol/l) and vitamin B12 values, and high PTH (44.3 pmol/l) and bone markers. Densitometry (DXA) showed characteristics for severe osteoporosis. The diagnosis of osteomalacia was made, and therapy with calcitriol (2 µg/day), calcium (CaCO$_3$ 3 x 1 g), vitamin B12 and folate was introduced, with significant clinical improvement. Other patient was 39 years old, admitted due to chronic bone pain and suspected bone metastases on scintigraphy. Medical history revealed cerebral palsy, epilepsy and chronic gastritis. Diagnostic evaluation did not confirmed malignant disease, but hypocalcaemia (1.97 mmol/l) and hypophosphatemia (0.46 mmol/l) were found, TSH (7.72 mIU/l) and PTH (21.3 pmol/l) were increased, with low vitamin D (9.3 mmol/l) and high alkaline phosphatase (360 U/l). DXA showed low bone mineral density. Final discharge diagnosis were osteomalacia, hyperparathyroidism and megaloblastic anemia. Calcium (CaCO$_3$ 1 g) and vitamin D replacement therapy (4000–6000 drops/day) were started, with clinical and laboratory tests improvement.

Conclusion
Calcium, PTH and vitamin D disorders require detailed medical history, diagnostic evaluation and differential diagnosis. Adequate therapy, monitoring and follow up guarantee well treated and satisfied patient.

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**EP278**

**25-OH vitamin D: a predictor of clinical outcomes in primary hyperparathyroidism**

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Objectives
We aimed to find if there is any relationship between vitamin D levels and clinical, laboratory parameters and osteoporosis, in primary hyperparathyroidism (PHPT).

Material and methods
128 patients with PHPT and 30 patients as a control group were analysed. Patients with PHPT were grouped due to vitamin D levels and levels low than 20 µg/ml accepted as deficiency.

Results
Patients with 25-OH vitamin D < 20 µg/ml were younger ($P = 0.043$). Also they were more obese: BMI $\geq 30$ ($P = 0.18$) and more hypertensive ($P = 0.032$). Metabolic syndrome (MS) incidence was higher in the patients with 25-OH vitamin D levels < 20 µg/ml ($P = 0.44$). Incidence of thyroid nodules and thyroid nodule volume were similar between two groups. Also, fasting plasma glucose (FBG), HDL, LDL, triglyceride (TG), creatinine (Cr), glomerular filtration rate (GFR), TSH, T3, PTH, Ca, 24 h urinary Ca and neutrophil/lymphocyte ratio were similar. There was no significant difference in the incidence of nephrolithiasis, osteoporosis and parathyroid adenoma size between the groups. MS incidence was higher (32.8%) in PHPT ($P = 0.042$). 25-OH vitamin D was found to be associated with age, BMI, thyroid volume and triglyceride in regression analyses.

Conclusion
25-OH vitamin D levels may be an indicator of hypertension (HT) and MS in PHPT. It also may be used as a treatment target in the severe disease.

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**EP279**

**The diagnostic value of parathyroid hormone washout in primary hyperparathyroidism patients with negative or unequivocal 99mTc-MIBI results**

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Introduction
Primary hyperparathyroidism (pHPT) is a common endocrine disease mainly caused by single or multiple hyperfunctioning parathyroid lesions. In 2–7% of cases, surgery is not curative at first operation and reoperation is required. Ultrasonography and sestamibi scan are the most widely used methods for identification of the culprit parathyroid gland with the disadvantage of high false positives caused by other cervical pathologies. Herein we aimed to search the diagnostic value of measurement of parathyroid hormone (PTH) concentration in the needle washout of suspicious lesions suggestive for parathyroid adenoma with negative or unequivocal MIBI results.

Methods
Our endocrine database was searched retrospectively for the patients with PHPT who underwent PTH washout. There were 100 lesions of 70 patients. Among them, 21 lesions in 16 patients were operated and data of these lesions were analysed. All patients had at least one suspicious parathyroid lesion detected by ultrasonography and all patients were evaluated by 99mTc-MIBI.

Result
The mean age of the patients was 53.3 ± 10.6 years with the majority of them being female (87.5%). The mean preoperative serum calcium level was 11.04 ± 0.33 mg/dl. The median serum PTH level was 140 pg/ml (ranging from 55 to 371) and the median serum PTH washout level was 3316 pg/ml ranging from 13 to 5000. Preoperatively 99mTc-MIBI scan was negative or unequivocal in 15 of 21 operated lesions while it was positive in six. For the lesions that the MIBI failed to localise, the sensitivity of PTH washout was 91% and the specificity was 66%.

Conclusion
PTH washouts can contribute significantly in establishing the parathyroid nature of cervical lesions that has conflicting preoperative sestamibi results and also might help the surgeon to perform a more successful operation.

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EP280  
Proximal femur strength, cortical thickness and bone structure in Klinefelter syndrome

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Introduction

Klinefelter syndrome patients (KS) frequently show low bone mass, which could have multiple aetiologies. The structural basis of low bone mass and its consequences on bone strength are almost not known, but analogies in bone microstructure and strength between KS and ageing women have been proposed by studying distalibia by HRpQCT. The aim of this study was to compare proximal femur strength and bone structure of KS with elderly women and men.

Patients and methods

Proximal femur QCT analysis was performed on 18 KS (mean age 44 ±8 years) and compared with 89 elderly women (76 ±6 years) and 39 elderly men (79 ±5 years). QCT-based estimates of proximal femur strength were obtained with a personalized Finite Element procedure previously validated in-vitro and in-vivo under loading conditions corresponding to ten fall directions to span accidental conditions. Bone structure analysis included trabecular and cortical volumetric bone mineral density (Tb.vBMD, Ct.vBMD), and cortical thickness (Ct.Th.), mapped to 18 sectors covering the whole femoral neck. Femoral neck length and cross-sectional area were calculated.

Results

KS and women had similar bone strength (KS: 2981 ±514 N, W: 2822 ±627 N, Mann–Whitney P = 0.14), both significantly lower (P <0.001) than elderly men (4176 ±985 N). Bone cortex was significantly thinner in KS patients with respect to women (P <0.05 in 13 out of 18 sectors). Ct.vBMD was equivalent in KS and women, whereas Tb.vBMD was instead higher in KS (P =0.003). Femoral neck was significantly larger in KS patients (CSA 25% higher, P <0.001).

Conclusion

We showed for the first time that, at proximal femur, KS and elderly women are similar in terms of bone strength. This similarity emerged however from different structural traits: KS had thinner femoral neck cortex, partially compensated by a denser trabecular compartment and larger bone dimensions (i.e. higher moments of area and bone mass).

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EP281  
18F-fluorocholine as PET tracer to localize the dominant source of PTH in a patient with X-linked hypophosphataemia and hyperparathyroidism

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Introduction

18F-fluorocholine is a PET tracer used in the diagnostic work-up of patients with prostate cancer but was incidentally found to detect other tumours such as meningiomas, pituitary and parathyroid adenomas. 18F-fluorocholine PET/MRI is currently under investigation as an imaging tool for detecting hyperfunctioning parathyroid glands in primary or secondary hyperparathyroidism, especially in patients qualifying and willing to undergo parathyroid surgery where standard diagnostic localization procedures such as neck ultrasound and scintigraphy failed to localize an adenoma. Case report

A male patient was diagnosed with X-linked hypophosphataemic rickets at the age of 5 years with severe dwarfism and leg deformities. Treated with phosphate supplements and calcitriol (and several orthopaedic correction surgeries), he reached reasonable growth and height, with at least partial correction of mineralization deficit and without obvious kidney damage. As expected, tubular phosphate reabsorption (TmP/GFR) remained low (<0.4 mmol/0) and FGFR3 remained high. At the age of 23 years, he developed hypercalcaemia which persisted after treatment (including calcitriol) was stopped, i.e. a laboratory constellation of primary hyperparathyroidism. However, both neck ultrasound and dual-isotope 99mTc-Tc-te trof osmin and 123I sodium iodide SPECT failed to localize an adenoma. Since the patient and his physicians preferred surgery (rather than cinacalcet) when feasible with maintaining normal parathyroid function, the patient consented to off-label imaging with 18F-fluorocholine PET/MRI, revealing intense focal tracer accumulation at the right lower position. Minimally invasive videoassisted selective parathyroidectomy was performed, resulting in an intraoperative drop of PTH from 258 to 73 ng/ml and subsequent normalization of serum calcium. Calcium and PTH remain normal for more than a year of follow-up, up to this writing.

Conclusion

Our finding suggests that 18F-fluorocholine PET/MR can be a helpful and sensitive tool to localize the dominant source of PTH in difficult selected cases where minimally invasive selective parathyroidectomy is considered the treatment of choice.

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EP282  
A prospective study on juvenile primary hyperparathyroidism population

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Primary hyperparathyroidism (PHPT) is a common disorder in adults but is uncommon in young people and features of juvenile PHPT (J-PHPT) are debated in literature. The aim of the study was to evaluate the characteristics of PHPT in juvenile sporadic (S) and familial (F) patients. It’s a monocentric prospective study at a referral centre in 154 patients with ≤20 years. Patients were evaluated at diagnosis and at the last follow-up visit (median follow-up 2 years), comparing clinical presentation, biochemical, densitometric, histological parameters, percentage of cure after parathyroidectomy (PTx) between S and F. One hundred-twelve patients had SJ-PHPT, 31 patients had multiple endocrine neoplasia type 1 (MEN1) syndrome and 11 familiar isolated hyperparathyroidism (FIHP). Symptomatic nephrolithiasis was observed in 44% of SJ-PHPT and in 48.4% of FJ-PHPT and aspecific neuropsychic symptoms in 95% of all patients. Ninety SJ-PHPT and 27 FJ-PHPT underwent PTx. The histology showed in SJ-PHPT and FJ-PHPT respectively: a single adenoma in 86 and seven patients, hyperplasia in two and 19 patients, carcinoma in one SJ-PHPT and exploration without excision of parathyroid tissue was observed in one SJ-JPHPT and one FJ-PHPT. Ionized serum calcium and PTH significantly decreased after PTx in both group. The persistence/recurrence rate of disease was 15% in sporadic cases and 52% in familial cases. There were not statistically significant differences in biochemical and densitometric markers between sporadic and familial group. In both groups males showed a more statistically significant (P <0.001) severe PHPT for both biochemical and densitometric markers. When the overall patients were stratified for age ≤25 and >25 years, younger patients appeared to have a significantly (P <0.001) more severe disease.

In conclusion, J-PHPT is generally a more severe disease in males; it has a higher rate of persistence/recurrence disease, even in sporadic patients; S and F patients show similar features.

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EP283  
Outcome of subtotal parathyroidectomy in patients with renal hyperparathyroidism

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Introduction

Hyperparathyroidism is common in patients with end-stage renal failure (ESRF): up to 20% require treatment for hyperparathyroidism within 10 years of commencing haemodialysis. Despite the significant cost of long-term medical treatment with calcimimetics and poor patient compliance, only a minority of patients are referred for surgery, usually due to their significant co-morbidity.

Methods

Outcome data of patients with secondary or tertiary hyperparathyroidism undergoing subtotal parathyroidectomy in our department from 2012 to 2014 were reviewed. All patients underwent bilateral neck exploration with nerve monitoring. Serum parathyroid hormone (PTH) and calcium levels were measured postoperatively.
Results
25 patients (median age 52 years) underwent subtotal parathyroidectomy. 18/25 patients (72%) had ESRF and secondary hyperparathyroidism whilst 7/25 patients (28%) had post-transplant tertiary hyperparathyroidism. The majority of patients had evidence of osteopenia or osteoporosis on bone densitometry and 17/25 patients (68%) had some degree of hypercalcemia at referral. At least four parathyroid glands were identified intra-operatively in 19/25 patients (76%) and a subtotal procedure was performed, leaving ~ 50 mg of parathyroid tissue in situ. In 6/25 patients, three or fewer parathyroid glands were identified, and in these patients all the identified glands were excised. 24/25 patients (96%) had serum PTH levels <14 pmol/l at most recent follow up (range 3–24 months). Normocalcaemia was achieved in 16/17 (94%) of the patients who were hypercalcaemic pre-operatively. Post-operative complications included severe transient hypocalcaemia requiring i.v. calcium infusion in two patients, and one patient required emergency reoperation for bleeding. One patient experienced temporary unilateral recurrent laryngeal nerve palsy which recovered fully within 3 months post-surgery.

Conclusion
Subtotal parathyroidectomy can deliver biochemical success in >90% of patients with renal hyperparathyroidism. It offers a safe and cost-effective alternative to total parathyroidectomy.

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EP286
Thalassemia-induced osteoporosis and bisphosphonate treatment: a systematic review and meta-analysis
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Introduction
Osteopenia and osteoporosis develop with aging in thalassemia patients despite clinical treatment therapy has improved. Bisphosphonates, which are potent inhibitors of osteoclastic bone resorption, have been recently used to correct the bone abnormality in thalassemia with encouraging results. Bisphosphonates are a class of drugs that prevent the loss of bone mass, used to treat osteoporosis and similar diseases. They are the most commonly prescribed drugs used to treat osteoporosis. Bisphosphonates act by inhibiting osteoclastic recruitment and maturation, preventing the development of monocyte precursors into osteoclasts, inducing osteoclast apoptosis and interrupting their attachment to the bone.

Scope
The scope of the present work was to meta-analyse available data concerning the role of bisphosphonates in thalassemia-induced osteoporosis.

Methods
A search was carried out to find relevant studies and reviews published up to date. The database used was Pubmed. The MeSH terms used were: bisphosphonate, thalassemia and/or anaemia, osteoporosis, which yielded 33 results. From those 22 has been selected for further processing as more relevant to the topic of study.

Based on the meta-analysis of selected studies it appeared that bisphosphonates could prove an effective treatment for osteoporosis. In particular, zoledronic acid was effective in the treatment of osteoporosis, while clodronate did not appear to be equally effective. In total, bone mineral density as well as markers of bone turnover were effective in the treatment of thalassemia-induced osteoporosis.

Conclusions
Cross-examination of several studies suggests that bisphosphonates are to be considered as a therapeutic option for the treatment of thalassemia-induced osteoporosis.

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EP285
Low extracellular sodium promotes adipogenic commitment of human mesenchymal stromal cells: a novel mechanism for chronic hyponatraemia-induced bone loss
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Hyponatraemia represents an independent risk factor for osteoporosis and fractures, affecting both bone density and quality. A direct stimulation of osteoclastogenesis and bone resorption in the presence of reduced extracellular sodium concentrations ([Na+] ) has been shown, but, to date, the effects of reduced [Na+] on osteoblasts have not been elucidated. This study investigated the effects of a chronic reduction of extracellular [Na+] , independently of osmotic stress, on human mesenchymal stromal cells (hMSC) from bone marrow, the common progenitors for osteoblasts and adipocytes. As regards hMSC homeostasis, we found a significant inhibition of adhesion and viability, but no alteration of their surface antigen profile and immuno-modulatory properties.

Low extracellular [Na+] were able to modulate the osteoblastic production of factors (MCP-1 and CXCL-12) that stimulate osteoclast recruitment and bone resorption. Next, we tested whether chronic hyponatraemia was able to alter the cellular commitment of hMSC. We found that hMSC maintained their ability to commit toward the osteogenic and the adipogenic phenotypes, as demonstrated by the unaltered gene expression of specific differentiation markers. However, the dose-dependent increase in the number of adipocytes as a function of reduced [Na+], observed by Oil-Red-O staining, suggested a preferential commitment toward the adipogenic phenotype at the expense of osteogenesis. This observation was further supported by the amplified inhibitory effect on the expression of osteoblastic markers exerted by adipocyte-conditioned media in low [Na+] conditions. Finally, the analysis of cytoskeleton by immunofluorescent microscopy showed that low [Na+] was associated with disruption of tubulin organization in hMSC-derived osteoblasts, thus suggesting a negative effect on bone quality. These findings add new evidence that hyponatraemia is to be carefully taken into account by clinicians because of its negative effects on bone, in addition to the known neurological effects, and indicate for the first time that impaired osteogenesis may be involved.

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Pseudohypoparathyroidism type 1a (PHP1a) is a disorder characterised by resistance to the biological actions of circulating parathyroid hormone (PTH) along with typical features of Albright’s hereditary osteodystrophy (AHO). Tissue-specific imprinting of GNAS gene results in complete resistance to PTH in renal proximal tubule, but skeletal responsiveness to PTH appears intact, since Gnas is biallelically expressed in human bones. The objective of this study was to determine BMD, and its relation to PTH levels in a group of young adult patients with PHP1a (age range 19–32 years). BMD measurements (Hologic QDR 4500) at the lumbar spine (LS), total hip (TH) and femoral neck (FN) were obtained in five patients with PHP1a (diagnosis was based on presence of AHO features combined with multihormone resistance). All patients were diagnosed with this condition earlier, and treatment was begun between ages 4 and 21 years. Characteristics of study patients: intact PTH levels ranged from 120.9 to 436 pg/ml (reflecting inadequate dosing of calcium and calcitriol); all patients were taking levethracen and TSPL levels were mildly elevated (range 5.98–12.10 µM/mL); three subjects were GH deficient, and none received GH therapy. The mean BMD Z-score for the LS was −1.4 (range −2.0 to −0.6), which is not significantly different from normal. Three subjects had Z-scores of less than 1.3 expected for the healthy population, and one of them met the criteria for low BMD. The mean BMD Z-score for the TH was −1.1 (range −1.6 to −0.8), and for the FN was −0.8 (range −1.9 to 0.2), both not significantly different from normal controls. Our results show that subjects with PHP1a, despite significant secondary hyperparathyroidism, had normal bone mass, with exceptions of one subject (20%) who had low LS BMD. These results are somewhat conflicting with previous study which demonstrated that bone mass is either normal or increased in PHP1a.

Results

Mean T-score for the LS was −1.4 (range −2.0 to −0.6), which is not significantly different from normal. Three subjects had Z-scores of less than 1.3 expected for the healthy population, and one of them met the criteria for low BMD. The mean BMD Z-score for the TH was −1.1 (range −1.6 to −0.8), and for the FN was −0.8 (range −1.9 to 0.2), both not significantly different from normal controls. Our results show that subjects with PHP1a, despite significant secondary hyperparathyroidism, had normal bone mass, with exceptions of one subject (20%) who had low LS BMD. These results are somewhat conflicting with previous study which demonstrated that bone mass is either normal or increased in PHP1a.

Conclusions

The most important predictors for osteoporosis in our study were type 1 diabetes duration (over 10 years) and the presence of diabetic nephropathy. Age towards the upper limit of inclusion (i.e. 55 years old) or low BMI values (low/normal) may complete an indication for performing DXA in type 1 diabetic patients. Long-term lifestyle measures that we found to be protective for osteoporosis were: avoiding coffee and alcohol consumption, regular exercise and an optimal metabolic control of diabetes.

Disclosure

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EP288

Clinical risk factors for osteoporosis in type 1 diabetes

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Introduction

Type 1 diabetes secondary osteoporosis is an underdiagnosed condition and there are few studies that addressed the topic of clinical risk factors in this context, although, for a better diagnosis and management, it is of great importance to find such predictors.

Aim

To evaluate bone mineral density and parameters of bone metabolism in patients with type 1 diabetes in comparison with a group of healthy subjects and to determine possible risk factors for osteoporosis in the context of type 1 diabetes.

Patients and methods

102 patients with type 1 diabetes and 59 healthy controls (pre-menopausal women and men, aged between 20 and 55 years), matched by age, sex, and BMI were included in the study. All subjects with secondary causes of osteoporosis except type 1 diabetes and diabetic patients with stage 3 nephropathy or more (GFR < 60 ml/min per 1.73 m²) were excluded. Their lifestyle, personal and parental history were evaluated with a questionnaire, anthropometric measurements were made and DXA osteodensitometry was performed. Serum osteocalcin, intact PTH, 25(OH) vitamin D, total calcium, phosphorus and magnesium were determined.

Results

The risk for low BMD (at least a Z score equal or lower than −2.0 S.D. at any site) was 1.2 higher in type 1 diabetes (95% CI 0.43–3.33), however BMD was not significantly different between patients and controls (P = 0.08 for lumbar spine and 0.56 for femoral neck). Type 1 diabetic patients had a median age of 28 and a median disease duration of 11.5 years. Median HbA1c was 8.1%. BMD for a disease duration over 10 years was significantly lower than that for 0.5–5 years (P = 0.008, ANOVA). Diabetic nephropathy (stages 1 and 2) increased the risk for low BMD and was associated with a significant rise of PTH. Age was negatively associated with lumbar spine BMD and positively with PTH. BMI was positively associated with BMD at all sites.

Conclusions

The most important predictors for osteoporosis in our study were type 1 diabetes duration (over 10 years) and the presence of diabetic nephropathy. Age towards the upper limit of inclusion (i.e. 55 years old) or low BMI values (low/normal) may complete an indication for performing DXA in type 1 diabetic patients. Long-term lifestyle measures that we found to be protective for osteoporosis were: avoiding coffee and alcohol consumption, regular exercise and an optimal metabolic control of diabetes.

Disclosure

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Glucocorticoid induced osteoporosis: can we do more to prevent it?

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Introduction

Osteoporosis is a well-known and extremely debated side effect of glucocorticoid therapy being able to generate vertebral fractures even at low doses. Our study highlights the need for better prevention through improved doctor-patient communication and correct implementation of available screening tools.

Methods

Since August–December 2014 we distributed to 85 rheumatic patients a self-completed questionnaire. We recorded patient data and their awareness on current recommendations, osteoporosis screening/treatment information. Hospital’s electronic database provided DXA and radiographic results.

Results

Study included 72/85 women, median age 57.5 years, 38/85 rheumatoid arthritis, 20/85 systemic lupus erythematosus, and 27/85 other diseases, median disease duration 72 months. 55/85 (64.70%) received < 7.5 mg/day, whilst 30/85 (35.29%) received > 7.5 mg/day for > 3 months. 40/85 (47.05%) have undergone a DXA and 24/40 (60%) have osteoporosis and bisphosphonate treatment. Only 51/85 (60%) is aware of this therapy risk. FRAX 10 years probability of osteoporotic fractures was > 20% in 9/24 (37.5%) patients. Only 31/85 (36.47%) were aware that smoking cessation is recommended. 62/85 (72.94%) knew excessive alcohol intake must be avoided and 20/85 (23.52%) were aware of the need for weight-bearing activities. Only 50/85 (58.82%) have a radiographic imaging of the spine and 10/50 (20%) have vertebral fractures on radiography. 70/85 (82.35%) have received vitamin D supplements.

Conclusion

Study revealed a lack of proper screening for glucocorticoid osteoporosis and a high percentage of patients not aware of existing recommendations regarding lifestyle modifications needed for prevention. Clinicians should make more efforts for patient to properly understand this risk, to know the ways to diminish it and, last but not least, the utility of early diagnostic and treatment.

Disclosure

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EP290

Barakat syndrome: an uncommon cause of hypecalcaemia

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Identification and management of patients with Barakat syndrome is important in the clinical practice.
Introduction
Barakat syndrome is a very rare disease and an uncommon aetiology of hypocalcaemia. Also known as HDR syndrome it is an autosomal dominant disorder characterised by hypoparathyroidism, sensorineural deafness and renal disease.

Clinical case
A 59-year-old Caucasian woman was admitted to our Endocrinology ward in May 2014 due to hypocalcaemia despite being medicated with oral calcium. At 35 years old a diagnosis of hypoparathyroidism was established in another hospital when she presented generalised seizures and cardiac failure. Intracranial basal ganglia calcification where revealed at that time and a diagnosis of hypocalcaemic miocardiopathy was established. At the present admission in our hospital, further history revealed progressive hearing loss for the last 20 years. Laboratory work up: Ca2+ 7.7 mg/dl (8.6–10.2 mg/dl), Pi 3.1 mg/dl (2.5–4.5), Mg2+ 1.9 mg/dl (1.6–2.3), PTH 1.3 pg/ml (12–88), and creatinine 1.10 mg/dl. Abdominal CT scan showed right kidney hypoplasia. DNA sequence analysis revealed on exon 5 of GATA3 gene a heterozygote mutation c.1043T>G (p.Leu348Pro) that confirmed the diagnosis of Barakat syndrome. We observed one of the two adult sons and the adult daughter of this patient. Hypocalcaemia due to hypoparathyroidism and neurosensorial bilateral deafness were documented in both. Genetic study of this offspring is in course.

Comments
Barakat syndrome may present a variable phenotype. Renal manifestations are the most heterogeneous and usually determine disease prognosis. This patient has the classical triad. The severity of hypocalcaemia since young age and subsequent irreversible cardiac involvement were determinant for prognosis. Timely diagnosis and appropriate hypocalcaemia treatment are paramount. Genetic screening of relatives takes particular relevance in this context.

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**EP291**

The diagnostic value of parathyroid hormone washout after fine-needle aspiration in patients with primary hyperparathyroidism

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Introduction
Commonly used pre-operative methods (ultrasonography and sestamibi scan) to localize the culprit parathyroid gland(s) in patients with primary hyperparathyroidism (PHPT), frequently yield false positive or false negative results. Parathyroid hormone (PTH) washout after fine-needle aspiration (FNA) may allow for a targeted surgical approach. The aim of this study was to test the diagnostic value of preoperative PTH washout after FNA in PHPT patients.

Methods/design
Retrospective study conducted in a tertiary centre. Ultrasound-guided FNA was performed if a structure compatible with a parathyroid adenoma was found on cervical ultrasound. A PTH washout cut-off value was considered diagnostic if performed if a structure compatible with a parathyroid adenoma was found on cervical ultrasound. A PTH washout cut-off value was considered diagnostic if

Results
Twenty-nine patients (2 (6.8%) males, mean age 58.6 ± 9.1 years) were included. Mean pre-operative serum PTH levels were 194.2 ± 176.8 pg/ml (normal: 10–53), while serum calcium and 25-hydroxy-vitamin D levels were 11.5 ± 1.4 mg/dl (normal: 8.8–10.6) and 24.1 ± 20.5 ng/ml (deficiency: < 20 ng/ml) respectively. Post-operative serum PTH and calcium levels were 45.9 ± 26.3 pg/ml and 9.04 ± 0.7 mg/dl respectively. A single adenoma was identified in 26 (89.7%) patients and a double adenoma in 1 (3.4%). Two (6.9%) patients were harbouring an ectopic parathyroid adenoma (upper mediastinal and intra-thyroidal). Twenty-four patients (82.7%) had elevated PTH washout concentrations (mean values: 2009.5 ± 1417.6 pg/ml). True positive and false negative results were 24 and 4 respectively. The specificity, sensitivity and positive predictive value (PPV) were 88.51, 100, and 100% respectively. Interestingly, in ten out of 12 patients with a negative sestamibi scan, the PTH washout yielded a truly positive result.

Conclusions
Elevated PTH washout concentrations after ultrasound-guided FNA is a highly accurate diagnostic tool in identifying parathyroid adenomas and guiding parathyroid surgery.

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**EP292**

Relationship between vitamin D supply and healing in patients with hip fracture

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Background
Vitamin D (VD) deficiency is important risk factor of fractures. Yet, the relation of serum 25-hydroxyvitamin D (25(OH)D) levels and recovery of fractures is poorly studied. Our aim was to investigate the VD supply in hip fractures also with regard to lifestyle and other clinical (malignancy, kidney and liver disease, osteoporosis) conditions.

Method
25(OH)D (protein binding assay, Cobas, Roche) and parathyroid hormone (PTH) (electrochemiluminescence immunoassay, Cobas, Roche) levels of 202 patients (67 men and 135 women) with hip fracture (age 75 ± 12 years) and 102 age-matched persons with active lifestyle, as controls were investigated.

Results
VD deficiency and secondary hyperparathyroidism occurred significantly more frequently in patients with hip fracture than in the control group (73% vs 36% and 33% vs 12% respectively). Patients with better condition after surgery showed significantly higher 25OHD median with interquartils ranges: 44 (26–72) vs 15 (9–43) nmol/l; P < 0.001) and lower PTH (51 (35–64) vs 63 (48–88) pg/ml, P < 0.05) levels than patients with bad condition. 31 patients who died after surgery (median survival time: 19 (5–52) days) had lower 25OHD levels than those who survived (23 (9–43) vs 33 (17–57) nmol/l) without significant difference in PTH levels. These results were independent of chronic disorders.

Conclusion
The correlation between 25OHD levels and better postoperative condition confirm the importance of VD substitution in prevention, as well as in healing, and in increased survival rate.

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**EP293**

An oral high dose of cholecalciferol restores vitamin D status in deficient postmenopausal HIV-1 infected women independently of protease inhibitors therapy

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Introduction
The best repletion and maintenance dosing regimens with cholecalciferol in vitamin D deficient HIV-1 patients remain unknown. Protease inhibitors (PIs) have been shown to inhibit vitamin D 1α- and 25α-hydroxylation in hepatocyte and monocyte cultures. We therefore evaluated the effect of a single high dose of cholecalciferol in vitamin D deficient HIV-1 postmenopausal women undergoing treatment with highly Active Anti-Retroviral Therapy (cART), with and without PIs.

Methods
Forty HIV-1 postmenopausal women treated with cART, with hypovitaminosis D (<20 ng/ml), were enrolled. We measured serum changes of 25-hydroxyvitamin D (25(OH)D), 1.25-dihydroxyvitamin D (1.25(OH)2D), parathyroid hormone (PTH), serum calcium and urinary calcium excretion following a loading dose of 600 000 IU of cholecalciferol after 3, 30, 60, 90, and 120 days.

Results
The sample was divided according to the presence PIs (group A, n = 20) or absence (group B, n = 20). There were no significant differences between the two groups at baseline (mean 25(OH)D group A 13.93 ± 3.85 vs group B 12.94 ± 3.86 ng/ml, P = NS). The cART scheme was not modified during the study period. We did not find any significant changes in the two groups, as regards: the mean CD4 values, the HIV RNA values, and the body mass index. A significant increase in mean 25(OH)D and 1.25(OH)2D levels at day 3 and throughout the entire observation period was found in both groups (P < 0.001). PTH levels concomitantly decreased in both groups (P < 0.001). Mean albumin-adjusted serum calcium increases with respect to baseline were significant only at days 3 and 30 for both groups (P < 0.01). There were no significant differences between the groups at any time, by two-way RM ANOVA.

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negative mutation and leads to higher calcium levels than other known CASR mutations. Cinacalcet treatment lowered serum calcium to 2.95 mmol/l and the patient has not presented new pancreatitis episodes.

Conclusion
Parathyroid adenomas are the main cause of primary hyperparathyroidism. They are usually small – weighing <1 g – and not easy to find – requiring meticulous imaging studies for localisation. Giant adenomas are uncommon, large tumours and high levels of PTH raise the suspicion of parathyroid malignancy.

Case presentation
A 68-year-old female presented in our clinic with polydipsia, polyuria, nausea, weight loss, and extreme muscular weakness – she wasn’t able to walk – and depressive mood. Clinical exam revealed dehydration and right cervical mass. Calcium was 21 mg/dl and PTH was 2238 pg/ml. The patient was also vitamin D deficient – 25OH vitamin D 14 µg/l. Radiographic study showed fracture of the first lumbar vertebra, CT scan showed multiple osteolytic areas of the skull. Osteodensitometry demonstrated osteoporosis (lumbar spine T score −2.9 s.d. and distal radius T score −6.7 s.d.). Ultrasonography revealed a hypoechogenic inhomogeneous mass, 38/30/45 mm, laterally and caudally to the right thyroid lobe. Parathyroid scintigraphy (99mTc-MIBI) demonstrated a large area of high uptake in that region. The patient received intravenous fluids, loop diuretic, i.v. bisphosphonate (zolendronate) and calcitomin to reduce the level of calcium, then she was successfully operated. Calcemia dropped after surgery and it was managed with i.v. calcium and alpha calcidol. Mild hypocalcaemia persisted for more than 6 months thereafter and so did the high levels of PTH, that raised to 506.5 pg/ml, then returned to normal – the hungry bones syndrome. The pathologic diagnosis was benign parathyroid tumour – parathyroid adenoma.

Conclusions
This is a rare case of giant parathyroid adenoma. The peculiarities of the case are the size of the tumour, the very high level of calcium and PTH – suggesting a malignant tumour, and the persistence of high levels of PTH and hypocalcaemia months after surgery.

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EP297
Primary hypoparathyroidism is common in adult patients with β-thalassemia and protect patients from osteoporosis
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Introduction
β-thalassemia (βT) is associated to several endocrine abnormalities mainly due to iron overload. With the increase in βT-patients life expectancy, due to progresses in iron chelation therapy, more patients enter into adulthood than in the past and the prevalence of osteoporosis diseases is being reconsidered. The aim of the study is to investigate the prevalence of primary hypoparathyroidism (pHPT) in adult βT-patients and to characterize the relative clinical phenotype with particular regard to bone health.

Methods
We enrolled 26 adult patients with major or intermedia βT (12M and 14F; mean age of 38.1 ± 7.5 years). Serum PTH, 25-hydroxyvitamin D (25OHID), calcium, phosphorous, albumin, bone turnover markers, and bone mineral density (BMD) by dual-energy X-ray absorptiometry (Hologic) at lumbar and femoral site were measured.

Conclusions
An oral dose of 600 000 IU of cholecalciferol in HIV-1 postmenopausal women rapidly increases 25(OH)D and 1,25(OH)2D levels reducing PTH levels, regardless of the presence of PTH in the eART scheme.

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EP294
May the polymorphism of low molecular weight protein tyrosine phosphatase modulate metabolic and bone remodelling parameters associated with osteoporosis?
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Aims
To study the association of protein tyrosine phosphatase (LMPW-PTP/ACP1) polymorphism with bone mineral density and metabolic parameters of bone remodelling.

Methods
BMD (g/cm²) was measured by DEXA in 760 subjects: 448 normal BMD (359F/89M; 49.7 ± 12.9 years; 30.2 ± 5.4 kg/m²) and 312 osteoporosis (265F/74M; 63.9 ± 10.4 years; 27.16 ± 4.4 kg/m²). Metabolic bone remodelling parameters were assessed: LDL, HDL, total cholesterol, ALP, apo A-B, triglycerides, alkaline phosphatase (AP), and osteocalcin. ACP1 activity was measured by spectrophotometry. ACP1 polymorphism was evaluated by PCR.

Results
Association was found between the genetic polymorphism of ACP1 and its enzymatic activity with higher values for genotypes AC+BC, intermediate values for BB and lower values for AA + AB. Osteoporosis: i) increased LDL, total cholesterol, AP, osteocalcin and ACP1, and decreased HOMA; ii) association between genotypes BB+BC+AC (intermediate and higher ACP1 activity) and increased total cholesterol, LDL, and ACP1; and iii) positive correlation between AP and LDL, total cholesterol, and osteocalcin. Normal BMD: i) association between genotypes BB+BC+AC (intermediate and higher ACP1 activity) and increased ACP1 and decreased AP and ii) positive correlation between AP and osteocalcin and HOMA. Only correlations of AP with LDL and total cholesterol remained significant when analyzed separately AA + AB individuals.

Conclusion
In osteoporosis, ACP1 polymorphism appears to modulate some metabolic parameters associated with a decrease in BMD, including total cholesterol, LDL, and ACP1 activity.

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EP295
Pancreatitis in familial hypocalciuric hypercalcaemia
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Familial hypocalciuric hypercalcaemia (FHHC) is a characteristically asymptomatic condition that is caused principally by calcium sensing receptor gene (CASR) mutations and less frequently by GNA11 or AP2S1 mutations. We report a case of recurrent symptomatic pancreatitis in an FHH patient. The 17-year-old patient was hospitalized with abdominal pain and raised pancreatic enzymes due to acute pancreatitis. The only predisposing factor on investigation was a very elevated serum calcium level (3.3 mmol/l; NR: 2.15–2.60). This was associated with constantly moderately elevated PTH (33 ng/l; NR: 4–26), normal 25-OH vitamin D (44 ng/ml; NR: 30–80), elevated 1,25(OH)2 vitamin D (133 pg/ml; NR: 23–109), and undetectable urinary calcium. Family history revealed that the patient’s grandmother was also known to suffer from hypocalciuric hypercalcaemia, and that hypercalcaemia had been found in the patient’s mother, uncle, brother and sister. CASR sequencing revealed the patient (and family members) to be heterozygotic for a R185Q mutation, previously suggested to be a dominant
Postmortem studies have shown that a fifth parathyroid gland may be present in about 5% of patients with hyperparathyroidism. 1% of parathyroid glands are located in thyroid tissue. There’s a prevalence of 7–10% of thyroid ectopic tissue.

Case report
A 53-year-old male, submitted to bilateral nephrectomy due to a Grawitz tumour at the age of 25. Under haemodialysis since then (with a rejected renal transplant in the past), he was recently referred to our department with a tertiary hyperparathyroidism diagnosis. Treated intra-hemodialysis with alfalcacolor 0.25 μg and cinacalcet. Analytically had a PTH 1604 pg/ml, calcium 9.5 mg/dl, phosphorus 5.6 mg/dl, and creatinine 11.4 mg/dl. Cervical ultrasound did not identify parathyroid gland and thyroid scintigraphy suggested parathyroid adenoma in the bottom right. PET-scan showed bone lesions suggestive of brown tumours. The patient was submitted to surgery and has removed four parathyroid glands (9–20 mm) with an histology of ‘nodular hyperplasia of the parathyroid’.

Also, he had a history of bone osteoporotic fractures and both of them did not present pHPT. Bone turnover markers were not different in the two groups.

Conclusions
The prevalence of pHPT in adult bT-patients is higher if compared to that reported in literature on pediatric bT patients, the latter ranging from 8 to 11%. Moreover, we found an higher prevalence of pHPT compared to that reported in literature on pediatric bT patients. As expected, pHPT seems to exert a protective role on the development of osteoporosis in these patients.

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Introduction
Hypoparathyroidism is most commonly observed following neck surgery and is characterized biochemically by deficient parathyroid hormone (PTH) and hypocalcaemia alongside hyperphosphataemia and reduced 1,25-dihydroxyvitamin D. Standard treatment with oral calcium and vitamin D aims to maintain serum calcium within the low-normal range whilst avoiding hypercalcemia due to over replacement. However, concerns remain over the presence of hypercalciuria and the associated risk of renal calcification.

Aim
To assess whether serum and urine biochemical parameters are associated with the presence of renal calcification in hypoparathyroid patients on Alfacalcidol therapy.

Method
A 12-month audit of the laboratory database was undertaken of paired requests for 24-h urine calcium (24 h-Ca), spot calcium:creatinine ratio (Ca:Creat), serum calcium, phosphate, urea, and creatinine. A review of case notes was performed to confirm aetiology of hypoparathyroidism, Alfacalcidol dose and results of renal ultrasound scan (US3). Results
A total of 34 patients were identified as having hypoparathyroidism and receiving Alfacalcidol therapy. 24 h-Ca and Ca:Creat were not-normally distributed, however significant associations were found between 24 h-Ca and Ca:Creat when log-transformed (linear regression β-coefficient =0.64, 95% CI 0.36-0.92, P<0.001, β =0.63). 17 patients had documented hypercalciuria evidenced by elevated 24 h-Ca (five patients), Ca:Creat (eight patients), or both (four patients). 13 patients had undergone renal US3; four had evidence of renal calcification. Interestingly, these four patients each had an elevated Ca:Creat, in contrast with only one patient having elevated 24 h-Ca.No patient had hypercalcaemia. However, 20 patients had low, or low-normal serum adjusted calcium (Ca <2.2 mmol/l); nine of these patients having documented hypercalciuria evidenced by an elevated 24 h-Ca (78% of patients) or Ca:Creat (89% of patients).

Conclusion
Ca:Creat appears a sensible and convenient marker for the follow-up of patients on long term Alfacalcidol therapy to determine associated risk of renal calcification.

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Renal calcification in hypoparathyroid patients treated with calcium and vitamin D: can biochemistry help?
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Introduzione
L’ipoparatiroidismo è una condizione comune che si manifesta spesso dopo una chirurgia del collo e si caratterizza biochimicamente da una deficienza di paratiroid hormon (PTH) e ipocalcemia insieme ad iperfosfatemia e riduzione di 1,25-dihydroxyvitamina D. Il trattamento standard con calcio e vitamina D mira a mantenere il calcio sierico entro una gamma normale bassa, evitando ipocalcemia.

Oggetto
Oggetto
Il presente studio è progettato per valutare l’incidenza delle fratture ossee e il rischio associato. Sono state utilizzate le fratture di osteoporosi come indicatore della possibile presenza di calcificazioni renali.

Materiale e metodi
Un’auditoria a 12 mesi del laboratorio database è stata condotta per un periodo di 12 mesi, con la raccolta dei dati su 24 h-Ca, spot Ca:Creat, calcio sierico, fosforo e creatina. Una revisione di casi è stata effettuata per confermare l’aetiology dell’ipoparatiroidismo, la dose di Alfacalcidol e i risultati dell’ecografia renale (US3).

Risultati
Sono stati identificati 34 pazienti con ipoparatiroidismo e trattati con Alfacalcidol. 24 h-Ca e Ca:Creat non sono distribuiti normalmente, tuttavia sono stati trovati significativi rapporti tra 24 h-Ca e Ca:Creat quando sono stati effettuati log-transformazioni (coefficiente lineaer =0.64, 95% CI 0.36-0.92, P<0.001, β =0.63). 17 pazienti avevano documentata ipercalciuria evidenziata da elevati 24 h-Ca (cinque pazienti), Ca:Creat (otto pazienti), o entrambi (quattro pazienti). 13 pazienti avevano subito un’ecografia renale US3; quattro avevano evidenze di calcificazioni renali. Interessantemente, questi quattro pazienti avevano tutti un Ca:Creat elevato, in contrasto con un paziente solo con elevati 24 h-Ca. Nessun paziente aveva ipocalcemia. Tuttavia, 20 pazienti avevano livelli bassi o normali del calcio sierico corretto (Ca <2.2 mmol/l); nove di questi pazienti avevano documentata ipercalciuria, evidenziata da un elevato 24 h-Ca (78% dei pazienti) o Ca:Creat (89% dei pazienti).

Conclusione
Ca:Creat sembra un’indicazione sensibile e conveniente per la seguente di pazienti su terapia a lungo termine con Alfacalcidol per determinare il rischio di calcificazioni renali associato.

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A giant parathyroid cyst manifesting with a neck mass and hypercalcaemic crisis
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Introduction
Functional parathyroid cysts represent an uncommon cause of primary hyperparathyroidism (PHPT) and an even rarer cause of a cervical mass.

Case report
A 57-year-old woman was referred to our department following emergency treatment of hypercalcemic crisis (serum calcium 16.4 mg/dl) with i.v. hydration and zoledronic acid. She was found to have multiple vertebral fractures by plain radiographs one month previously. Despite being diagnosed and treated with cinacalcet for PHPT for a year prior to these events and a neck mass was noted, it was considered a cystic thyroid nodule. At presentation she had generalized weakness and left-sided neck discomfort with pressure symptoms. Her corrected serum calcium was 13.1 mg/dl, phosphate 0.9 mg/dl, PTH 330 pg/ml, alkaline phosphatase 260 (ULN 220 UI), and kidney function was normal. Past history was notable for partial thyroidectomy in the 1970s. On examination, a firm, fixed cervical mass was palpable from the sternal notch to the jaw angle. On ultrasound, the mass was cystic with various septa and measured 9 × 4 × 4 cm. Needle aspiration of the cyst evacuated 45 ml of hemorrhagic fluid, with PTH washout levels measuring 570 pg/ml. Within the next 2 weeks, a hematoma formed that resolved unevenly, but the cyst recurred almost to its original dimensions, again causing local pressure. At surgery, the cyst measured 6.4 × 4 × 4 cm and histology was consistent with hemorrhagic cystic necrosis of parathyroid adenoma surrounded by an intact thick (0.2–0.5 cm) fibrous capsule without evidence of local invasion. Postoperatively, serum calcium and phosphate were 8.6 and 3.8 mg/dl respectively. The patient remains normocalcemic on calcium and vitamin D supplementation 9 months after surgery.

Conclusion
This case highlights that a large functional parathyroid cyst can elude diagnosis because of its rarity; however, early identification is crucial for proper patient management.

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EP302
Observational study of PTH secretion dynamics in patients with secondary hyperparathyroidism
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The aim was to analyse dynamics of PTH secretion in dialysis patients during different period of observation and to determine factors of secondary hyperparathyroidism progression. We examined 92 patients, 52f, 40m; age 47.1 ± 11.4 years; dialysis duration 4.9 ± 3.9 years; mean observational period 8.9 ± 4.3 months (6–24). Serum PTH, 25(OH)D3, osteocalcin (OC), C-terminal telopeptide of type I collagen (β-CTX), alkaline phosphatase (ALP), calcium (Ca), and phosphorus (P) were measured initially and at the end of observation. All patients were recommended to follow low-phosphate diet and 74.4% received calcium carbonate. PTH level was 559.6 ± 552.5 initially and 603.9 ± 581.6 pg/ml at the end of observation, P = 0.251. Frequency of high, normal uremic and low PTH levels was 55.4% vs 57.6%, 20.7% vs 21.7% and 23.9% vs 20.7% respectively (P > 0.05). P decreased from 2.34 ± 0.67 to 2.14 ± 0.60 mmol/l, P = 0.0003. In patients with initial hypercalcemia PTH increased from 525.3 ± 518.4 to 616.2 ± 606.2 pg/ml, P = 0.03. PTH level at the end of observation correlate with age (r = −0.25), OC (r = 0.58), β-CTX (r = 0.76), and ALP (r = 0.40). Strong correlation was found with the initial PTH (r = 0.84). At the end of observation PTH decreased in 40 patients (43.5%), mean decrease 204.6 ± 250.1 pg/ml; increased in 52 patients (56.5%), mean increase 235.6 ± 274.5 pg/ml. Subgroups with decreased and increased PTH didn’t show differences of demographic data, levels of Ca, P, and bone turnover markers. Comparison of initial and repeated PTH level in subgroups with duration of observation 6, 9, 12, and > 12 months didn’t reveal significant changes. We can assume that in dialysis patients with stable parameters of Ca, P, and bone turnover markers no differences in bone turnover markers affect secondary hyperparathyroidism progression.

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EP303
Fragility fractures as the initial manifestation of indolent systemic mastocytosis
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Introduction
Systemic mastocytosis (SM) is a rare disorder characterised by clonal proliferation of abnormal mast cells in several tissues, most often skin and bone marrow. Indolent systemic mastocytosis (ISM) is the commonest disease variant in adults, characterised by very low rate of mast cell proliferation. SM has been recognised as a cause of secondary osteoporosis.

Objective
To evaluate bone mineral density and fragility fractures in ISM patients.

Methods
Fourteen patients (nine women and seven premenopausal), aged 27–63 years (43.4 ± 11.8) diagnosed according to World Health Organization criteria were studied retrospectively. Clinical and biochemical data and bone mineral density (BMD) measurements by dual X-ray absorptiometry at the lumbar spine, the total proximal femur and the lower one-third radius were analysed. T-score was used to define osteopenia (−1 to > −2.5 S.D.) or osteoporosis (≤ −2.5 S.D. or lower) in postmenopausal women or men older than 50 years, and z-score < −2.0 for low BMD in younger men and premenopausal women, according to the International Society for Clinical Bone Densitometry. No patient reported other diseases or use of treatments known to affect bone or mineral metabolism, at initial assessment.

Results
Two patients (14.3%) had osteoporosis, two patients (14.3%) had osteopenia and seven patients (50%) had low BMD. BMD was generally lower at the spine than at the hip. Three patients (21.4%) reported fragility fractures: a 43-year-old premenopausal woman and a 38-year-old man had vertebral fractures, while a 31-year-old premenopausal woman had non-vertebral fractures. None of the patients with fragility fractures had cutaneous mastocytosis and only one of them reported a mild episode of anaphylaxis.

Conclusion
Bone involvement is frequent in ISM patients and may be the initial manifestation. Osteoporotic fractures of unknown aetiology should lead to the suspicion of SM particularly in individuals younger than 50 years.

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EP304
Evaluation of clinical and biochemical features of patients with atypical parathyroid adenoma: a retrospective study
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Introduction
Primary hyperparathyroidism (PHPT) is usually caused by single or multiple adenomas and cancer is rare accounting for < 1% of all presentations. The presence of certain cytological and architectural features such as adherence to adjacent organs, a solid growth pattern, broad bands of fibrosis, cytological atypia, and an irregular growth contour do not indicate malignancy but are recognised as atypical features encountered more commonly in malignant than benign tumours. Tumours that demonstrate these atypical features and do not fulfill criteria for carcinoma can be classified as atypical adenomas. Herein we aimed to evaluate the clinical and biochemical features of the patients histopathologically diagnosed with an atypical parathyroid adenoma.

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EP305
Investigation of the relationship between type 2 diabetes and osteoporosis
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Introduction
Diabetes is often associated with complications and comorbidities. Osteoporosis (OP) is increasingly recognised as a significant comorbidity of type 2 diabetes mellitus (T2DM). The aim of this study was to determine the prevalence of OP in postmenopausal women with T2DM and to assess the association between T2DM and bone mineral density (BMD).

Methods
This cross-sectional study was carried out in 50 postmenopausal women with type T2DM and 50 age-matched non-diabetic women. Medical and lifestyle characteristics were recorded. BMD was measured in lumbar spine and femoral neck by dual-energy X-ray absorptiometry.

Results
Prevalence of OP in subjects with T2DM was 48%, whereas 30% of the non-diabetic subjects had OP (P = 0.002). Patients with lumbar and/or hip osteoporosis were older (P = 0.004), had a lower BMI (P < 0.001) and had a longer duration of disease (P < 0.001). BMD at the hip was positively correlated with BMI (P < 0.001). Age (P = 0.004), duration of diabetes (P < 0.001), mean HbA1c levels (P = 0.01), the presence of retinopathy (P = 0.04) were negatively associated with BMD at the hip and lumbar spine. No correlation was found between BMD and presence of microalbuminuria, neuropathy, peripheral artery disease, cerebrovascular event, and coronary artery disease.

Conclusion
We found a high prevalence of osteoporosis in postmenopausal women with T2DM. The insufficiency of insulin and the decreased insulin sensitivity are important causes for OP in the patients with T2DM.

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EP306
Intraoperative parathyroid hormone monitoring during parathyroidectomy: description of our clinical experience
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Introduction
Primary hyperparathyroidism is caused by a single adenoma in 85% of cases. This is why bilateral neck exploration seems to be a very aggressive procedure in a large number of cases. Intraoperative parathyroid hormone (IOPTH) monitoring could be a useful tool in primary hyperparathyroidism surgery allowing a less invasive surgical approach. The aim of our study is to evaluate the possible impact of the measurement of IOPTH during surgery.

Methods
Retrospective study in which we included all patients who underwent parathyroidectomy with IOPTH monitoring between 2008 and 2013. We considered the following variables: preoperative localization techniques; neck exploration (uni or bilateral); prediction of curative parathyroid resection by using MIAMI criteria (> 50% drop from highest baseline IOPTH level at 10 min after excision) and cure (normal calciumaemia 6 months after surgery). Subsequently, we compared this sample with a group of patients who underwent parathyroidectomy between 2000 and 2002 without IOPTH monitoring.

Results
We studied 115 patients (80.9% females; mean age 57.4 ± 14.1 years). In most cases Technetium-99m-sestamibi scintigraphy was the preferred localization technique (97.4% of patients) with positive result in 76.8% of scintigraphies. 76.5% of patients underwent unilateral neck exploration (100% of them were cured). Following MIAMI criteria we were able to predict curative resection in 97.2% of these patients. 93.9% of the total sample were cured after surgery. We compared this results with a series of 35 patients without IOPTH monitoring (74.3% females, 58.51 ± 9.1 years). We did not find significant differences in cure (93.9% vs 91.4%, P = 0.61). However, in the second group 100% of patients underwent bilateral neck exploration (23.5% in IOPTH group, P = 0.0005).

Conclusion
By monitoring IOPTH in focused parathyroidectomy it is possible to perform a less invasive surgical approach without reduction in cure rate.

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EP307
Hypercalcaemia in patient with primary hyperparathyroidism and acromegaly
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Introduction
Hypercalcaemia in acromegaly can be a result of several pathophysiological mechanisms. Multiple endocrine neoplasia type 1 (MEN1) syndrome, mitogenic effect of hyperactivated GH-parathyroid gland axis, i.e. primary hyperparathyroidism and hypercalcaemia mediated by elevated 1,25-dihydroxy vitamin D should be considered.

Case report
We describe a case of acromegaly associated with primary hyperparathyroidism. A 52-year-old female was diagnosed with acromegaly due to GH secreting pituitary microadenoma. Evaluation at diagnosis showed normal levels of hormones other than GH and IGF1, and presence of hypertension and multinodular goiter (volume 80 mm3). Because the patient denied surgery, treatment with cabergoline was administrated and a biochemical control was accomplished.

Within 1 year of the diagnosis laboratory data showed hypercalcaemia (serum calcium 1.51 mmol/l (1.10–1.40)) in the setting of elevated parathormone (PTH) levels (158 pg/ml (15–65)) and low levels of vitamin D (5.6 mmol/l (> 25)). Bone densitometry detected osteoporosis limited to the right radius (T score value = –4.0 s.d.). Analysis of 24 h urine showed normal calcium and phosphate excretion. This findings were consistent with diagnosis of primary hyperparathyroidism. Imaging and radioisotope studies identified enlarged thyroid gland, predominantly the left lobe with consequent tracheal compression, and higher radioisotope uptake in the lower pole of the left thyroid lobe. Surgical excision of left lower parathyroid gland and subtotal thyroidectomy was done. Histopathological examination confirmed hyperplasia of parathyroid and thyroid gland. After surgery, serum calcium normalised, PTH levels significantly reduced to 73.2 pg/ml. Vitamin D remained low (17.8 mmol/l) and TSH levels elevated to 27 mU/l (0.4–4) for which vitamin D and levothyroxine substitution was started.
EP308
The value of intraoperative sonographic evaluation of neck in primary hyperparathyroidism: case report of preoperative double adenoma upgraded to triple intraoperatively
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Background
Primary hyperparathyroidism (PHPT), caused by increased parathyroid hormone (PTH) secretion, leads to generalised disorder of bone metabolism characterised with hypercalcaemia and hypophosphatemia. Causes of PHPT include solitary parathyroid adenoma (80%), primary parathyroid hyperplasia (10–15%), and parathyroid carcinoma (1–2%). Other rare cause is double parathyroid adenomas (DPA) with frequency <1–2%, which can be sporadic or familial. DPA should be considered for persistent or recurrent PHPT cases.

Case report
A 45-year-old female patient with type 2 diabetes was admitted with weakness, fatigue, and generalized bone pain. She had a history nephrolithiasis five times in the last 2 years. In laboratory examination, serum calcium level was 12.3 mg/dl (8.8–10.6), phosphorus level was 2.9 mg/dl (2.4–5.1), albumin level was 4.1 g/dl (3.5–5.3), PTH level was 237 pg/ml (12–88), alkaline phosphatase was 99 IU/l (60–105 IU/l), 25-OH vitamin D level was 6.4 ng/ml (20–30 ng/ml), 24-h urine calcium was 483 mg/day, creatinine clearance was 75 ml/min, and prolactin level was 26 ng/m (5–26 ng/ml). I.v. saline and furosemide treatment was administered. Bone densitometry measurement showed osteoporosis. Neck ultrasound imaging revealed no abnormality in the thyroid gland with bilateral smooth, ovoid, hypoechoic lesion considered parathyroid adenomas at inferior contiguity of thyroid gland in size of 15 x 11.8 mm on the right and 18 x 12 x 7 mm on the left side. Tc99m-MIBI scan detected parathyroid adenoma in the lower part of the left thyroid lobe consistent with radioactivity uptake, while in the lower part of the right thyroid was suspicious. PTH level from fine needle aspiration material of parathyroid washout was measured 2097 pg/ml from the right side and 1989 pg/ml from left side. Hence, bilateral minimally invasive parathyroidectomy was intended to be performed, but the surgeon saw a third adenoma at retrosternal location by using intraoperative ultrasonography (US), all were removed and pathology report was consistent with parathyroid adenoma.

Conclusion
Intraoperative parathyroid evaluation by US plays an important role preventing patient from unnecessary surgery.

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EP309
Parathyroid hormone therapy for postoperative resistant hypocalcaemia
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Introduction
No consensus guideline on the treatment of hypoparathyroidism. Hypoparathyroidism is a disease characterized by hypocalcaemia and insufficient PTH.

Conventional therapy includes calcium and active vitamin D supplementation, often in large doses.

Case report
A 31-year-old woman presented with hypercalcemia. Serum calcium and phosphorus levels were 10.5 and 2.56 mg/dl respectively. The serum PTH level was increased (1619 pg/ml). The serum 25-OH vitamin D level was decreased (3.5 ng/ml). Her past medical history revealed osteoporosis (femur T score = −4.0). Parathyroid USG showed left and right parathyroid adenomas. Double adenoma excision from left and right inferior sites and total thyroideectomy was performed. On pathological examination of thyroid was benign thyroid nodules. Double parathyroid adenomas was identified. Postoperative serum calcium level was 5.5 mg/dl. She received daily calcium gluconate infusions. Discharge with calcitriol and CaCO3 with latest calcium level was 6 mg/dl. During follow-up, she was taken to internal medicine ward with symtomatic hypocalcaemia. Serum calcium, phosphorus, PTH, and 25-OH vitamin D levels were 5.2 mg/dl, 3.2 mg/dl, <3 pg/ml, and 5 ng/ml respectively. The doses were progressively increased up to 12 µg/day calcitriol. Under this treatment serum calcium level was 6.9 mg/dl. Phosphorus level was 3.8 mg/dl. Follow-up, 20 µg teriparatide b.i.d. was added to the treatment. She has used teriparatide for a period of 10 months. At the end of teriparatide treatment, calcitriol reduced to 4.5 µg/day and calcitrex D3 reduced 3×1 tb. Final control visit her calcium level was 8.5 mg/dl and phosphorus level was 4.1 mg/dl while taking calcitriol dose of 3.5 µg/day and calcitrex D3 dose of 2×2 tb.

Conclusion
In our postoperative hypocalcaemic case, calcitriol dose reduced and calcium level increased after the teriparatide treatment. Teriparatide may be useful in postoperative resistant hypocalcaemia.

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EP310
Vitamin D deficiency and bone health in patients with learning disability
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There is limited data on vitamin D status in patients with learning disabilities. As a group they possess multiple risk factors for vitamin D deficiency including limited access to sunlight, problems with mobility and anticonvulsant use. We reviewed the data for 105 patients with learning disabilities grouped according to the severity of learning disability (profound, severe, moderate, and mild). Data was available on vitamin D and calcium levels, dose of vitamin D3 needed to increase the vitamin D level above 80 nmol/l was 1945 units daily. Our data shows that in a group of patients with significant risk factors of vitamin D deficiency, the average dose of vitamin D needed to correct the vitamin D deficiency with the aim of correcting above a minimum target level of 80 nmol/l or 32 µg/l. There was a very weak negative correlation between baseline 25-vitamin D levels and the degree of learning disability (r = −0.14). There was no significant difference between the four groups before treatment, however there was a clear trend of higher vitamin D levels with a significantly higher post treatment vitamin D level in the profound learning disability group compared to those mild deficiency. The average dose of vitamin D3 needed to increase the vitamin D level above 80 nmol/l was 1945 units daily. Our data shows that in a group of patients with significant risk factors of vitamin D deficiency, the average dose of vitamin D needed to correct deficiency was on average a modest dose given the need for anticonvulsants. Indeed the response to treatment was greatest in the group who had the most profound disability.
Primary hyperparathyroidism (PHPT) is frequently diagnosed as an incidental finding of hypercalcemia. Overt bone disease (osteitis fibrosa cystica or brown tumor), with history of pathologic fractures is a rare presentation. A 48-year-old woman was admitted in with pain in the right thigh after a trivial fall. She also complained of generalized weakness and lethargy over the last 2 years. Her medical history mention multiple bone fractures in the last 6 years, namely left patella, both wrists and 4 years before surgery to lytic lesion of the right humerus, assumed as aneurysmal bone cyst. Her last follow-up CT, revealed recurrence of lytic lesion and she was propose to shoulder arthroplasty. Plain X-rays and CTs revealed pathologic fracture of the right femur, multiple osteolytic lesions (right humerus, right femur, both shoulder blades and iliac bones), subperiosteal erosions in the distal phalanges and old fractures in the ribs. Bone scan showed increased uptakes over the right humerus, right femur and tibia. Femur fracture was managed with osteosynthesis and lumbar biopsy documented multiple giant cells consistent with brown tumor of PHPT. Analysis revealed severe PHPT (serum calcium 3.49 mmol/l, phosphorus 0.53 mmol/l, and PTH 1435 ng/ml). Ultrasound showed an 5.8×3.9×2.4 cm mixed texture lesion in the left superior parathyroid and sestamibi scanning confirmed a left parathyroid adenoma, with a necrotic centre and bone uptakes coincident with previous bone scan. Considering patient’s age and high level of PTH, chest–abdomen CT were performed to excluded metastatic disease. Hereditary cancer syndromes were also considered. Treatment was initiated with hydration and zolendronic acid and parathyroidectomy was performed. Histopathology confirmed the diagnosis of parathyroid adenoma. Hungry bone syndrome developed following surgery and was necessary treatment with calcium carbonate and alfacalcidol.

Conclusion
Preoperative localisation with US, SS and US-FNA allows a minimal/unilateral surgical approach in 84% of the patients. Ultrasound is significantly more sensitive and accurate than SS and US-FNA, which have a high PPV. The performance of all localisation procedures decreases in parallel to adenoma size, with ultrasound still remaining most sensitive. US-FNA, although highly specific, is complicated by a relatively high rate of haemorrhagic and/or fibrotic changes in the biopsied adenoma and should be used cautiously.

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EP313
The effects of single high dose vs daily low dose oral cholecalciferal treatment on vitamin D levels and muscle strength in postmenopausal women

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Introduction
Vitamin D deficiency is a common health problem. Vitamin D supplements are used to improve vitamin D status. However, there are few data about what doses to give and how often to give. The aim of this study is to determine the effects of single high dose or daily low dose oral cholecalciferal (vitamin D3) on vitamin D levels and muscle strength.

Methods and design
60 healthy postmenopausal women who had serum vitamin D levels were <20 ng/ml were enrolled in the study in the winter and spring of 2013–2014. First group (n = 32) was given daily oral doses of 800 IU vitamin D3, second group (n = 28) was given single oral dose of 300 000 IU vitamin D3. Serum vitamin D levels and muscle strengths were measured at the beginning, 4th and 12th weeks. Muscle strength tests were performed at 60°s with Biodex system 3 isokinetic dynamometer.

Results
The mean vitamin D levels of first and second group at the beginning were 10.2 ± 4.4 ng/ml (9.7 ± 4.4 ng/ml (P = 0.37)), respectively. Significant increase in vitamin D levels was measured in both two groups at 4 and 12 weeks after vitamin D3 treatment. At 4th week the increase in single dose of vitamin D3 group (16.9 ± 5.8 ng/ml) (35.9 ± 9.6 ng/ml) was significantly higher than the daily low dose vitamin D3 group (35.9 ± 9.6 ng/ml) (P = 0.01). At 12th week the increase in single dose of vitamin D3 group (19.8 ± 7.2 ng/ml) (23.4 ± 4.7 ng/ml) was significantly higher than the daily low dose oral vitamin D3 group (23.4 ± 4.7) (19.8 ± 7.2 ng/ml) (P = 0.049). Quadriceps muscle strength score increased significantly in daily group at 4th week (P = 0.038). Hamstring muscle strength score increase significantly in daily group at 12th week (P = 0.037).

Conclusion
Although daily administration routes are effective in muscle strength, single administration is more effective in increasing vitamin D levels.

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EP315
The peripheral serotonin, the serum osteocalcin and CrossLaps: the assay in menopausal women

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Introduction
17th European Congress of Endocrinology 2015. The skeleton health is reflected by turnover markers as serum CrossLaps (CL), and by the calcium metabolism parameters (as ionic blood calcium, and, probably, by the 24-h urinary calcium excretion). The peripheral serotonin might have intra-normal levels in patients with osteoporosis but yet represents a part of the complex equation related to the bone homeostasis.

Aim
we analysed the bone parameters, including serotonin in relationship to the bone loss as reflected by central DXA.

Material and method
This is a transversal study in menopausal women, starting from 2009 up to the present. No patient with active neoplasia or with tumours history (including primary hyperparathyroidism) was included. The patients with osteoporosis or anti-resorptive therapy for osteoporosis were also excluded. The lumbar DXA (Prodigy) provided the bone mineral density (BMD), and the WHO criteria allowed the including the patients into the osteopenia or the normal group. The blood assay were ionic calcium, OC, CL (ELISA kit), serotonin (ELISA), parathormon (PTH), 25-hydroxy vitamin D or 25(OH)D, (chemiluminescence), the urinary assay was 24-h ca. Statistical significance (SS) was considered at P<0.05.

Results
55 women had osteopenia (N3=22), and normal DXA (N2=33). The ionic calcium was not SS different between the two groups (4.02 vs 3.92 mg/dl, P=0.23), neither PTH (42.6 vs 44.6 pg/ml, P=0.5), serotonin (155.36 vs 166.9 ng/ml, normal <440 ng/ml, P=0.55), 24-ur ca (0.14 vs 0.18 ng/ml, P=0.14), 25(OH)D (14.64 vs 13.52 ng/ml, P=0.5), BC, and OC are SS higher in osteopenia group vs normal: 0.49 vs 0.38 ng/ml (P<0.05), respective 25.68 vs 17.73 ng/ml (P<0.005).

Conclusion
Based on our observations, the bone turnover markers are higher in women with osteopenia vs normal, while the serotonin, or the calcium (regardless urinary or serum) and PTH are similar. Overall, a high prevalence of low 25-hydroxy vitamin D levels is found in menopause.

EP316
Vitamin D deficiency in acutely ill patients
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Introduction
Vitamin D deficiency has been reported to be widely found within the population. Vitamin D deficiency was also found to be prevalent in patients with autoimmune inflammatory diseases such as rheumatoid arthritis and systemic lupus erythematosus. Vitamin D deficiency was reported in almost all patients with acute myocardial infarction in a US multicenter study. Low concentrations of 25-hydroxyvitamin D (25(OH)D) are reported to be an independent risk factor for cardiovascular events, in particular for strokes and sudden cardiac deaths.

Aim
The aim was to study and report vitamin D levels in acutely ill patients being cared for in an acute care unit.

Methods
In 20 patients being cared for in an acute care unit and in 20 controls matched for age and sex 25(OH)D levels were measured. In the patient population CRP and procalcitonin were also measured. 25(OH)D was measured by RIA, normal values being 7.7–114 nmol/l.

Results
In the patients being cared for in the acute care unit 25(OH)D levels were 30.33±3.63 nmol/l (mean±S.E.M.), whereas in the controls 60.37±4.41 nmol/l (P<0.001, Student’s t-test). In the patients being cared for in the acute care unit vitamin D deficiency or insufficiency was found in 18 of the 20 patients.

Conclusions
Low vitamin D levels were found in patients hospitalised in an acute care unit. These findings are in agreement with findings of other investigators having reported low levels of vitamin D in patients with acute myocardial infarction. It has been proposed that low vitamin D levels may be a risk factor for cardiovascular events and in patients with acute myocardial infarction may predict adverse outcomes. It has also been proposed that vitamin D levels may decrease during the acute phase response, however, more studies are needed to confirm or refute this hypothesis.

EP317
The clinical profile of primary hyperparathyroidism: a single centre experience
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Introduction
Primary hyperparathyroidism is currently a frequent disorder. In the past primary hyperparathyroidism was diagnosed late in the course of the disease. With the introduction of routine calcium measurements, as well as the awareness of the disease amongst clinicians, the disorder is frequently recognized in asymptomatic patients. Thus, the clinical profile of primary hyperparathyroidism is changing.

Aim
The aim was to describe the clinical profile of primary hyperparathyroidism in a single hospital center in Athens, Greece.

Methods
The clinical presentation and clinical characteristics of patients with primary hyperparathyroidism being followed up in a single center in Athens are described. All patients had a complete biochemical profile. In all patients calcium, PTH and
25(OH)D3 were measured. In all patients thyroid and parathyroid ultrasonography was performed, as well as, parathyroid scintigraphy for the localisation of parathyroid tumors.

Results
In a single centre in Athens 35 patients with primary hyperparathyroidism are being cared for. Within this group of 35 patients, nine had mild primary hyperparathyroidism. Within this group of patients 12 were on treatment with cinacalcet for the management of the disease, whereas eight were on treatment with alendronate.

Conclusions
Primary hyperparathyroidism is a frequent disorder nowadays. As shown in the results of this study from a single center in Athens mild hyperparathyroidism is prevalent. Cinacalcet seems to be an option for patients not willing or not able to withstand surgery. Alendronate is another option for the pharmacological management of primary hyperparathyroidism, a drug treatment which aims to improve osteoporosis as well as calcium levels in patients with primary hyperparathyroidism.

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EP318
Raised calcium & PTH, not always a primary hyperparathyroidism
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Case
A 50-years-old gentleman underwent cardiac surgery which was complicated by postoperative arrhythmias and ischemic stroke. He was found to have raised calcium of 2.9 (2.2–2.6 mmol/l) subsequent to which PTH was tested and found to be raised at 342 (1.6–6.9 pmol/l) which increased to 41.2 pmol/l in few days. He was referred for work up and management of primary hyperparathyroidism. An USS of the neck showed 1.5 cm nodule posterior to left thyroid lobe and Sestimibi scan also showed increased tracer uptake on the left side, findings consistent with parathyroid adenoma. During the course of investigations, calcium increased to 3.4 mmol/l and he required hospital admission for acute management of hypercalcaemia. He underwent left parathyroidectomy for parathyroid adenoma but histology of the excised gland showed features consistent with Parathyroid Adenocarcinoma. He was investigated to look for metastases. The CT scan of chest and SPECT CT did not show local or distant Metastases. A repeat surgery was undertaken for left hemithyroidectomy which showed no local spread of carcinoma. The calcium and PTH normalized after the surgery until 6 months when PTH increased again up to 11.4 pmol/l but it was found to be associated with hypocalcaemia and low Vitamin D and improved with Vitamin D replacement. He has been having regular follow up and being monitored with calcium and PTH.DEXA bone scan shows improving bone density. There has been no recurrence for 6 years after the surgery.

Discussion
Parathyroid carcinoma is a rare malignancy with incidence of <1% among all hyperparathyroidism cases. There are no distinguishing features or investigations to differentiate adenoma from carcinoma. It is mostly diagnosed on histological examination of the excised parathyroid gland. Raising PTH with hypercalcaemia is usually suggestive of primary hyperparathyroidism but severe hypercalcaemia with markedly raised PTH should raise suspicion of Parathyroid Carcinoma.

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Diabetes (pathophysiology & epidemiology)

EP319
Insulin receptor substrate 1 and 2 genes polymorphisms are associated with metabolic syndrome but not cardiovascular risk factors in patients with metabolic syndrome
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Objective
The aim of our study was to investigate the relationships between insulin receptor substrat-1 (IRS-1) and insulin receptor substrat-2 (IRS-2) gene polymorphisms and cardiovascular factors such as blood pressures, BMI, LDL- cholesterol, triglyceride, HOMA-IR, homocysteine, hsCRP and fibrinogen levels in patients with metabolic syndrome (MetS).

Subjects and methods
The study population included 100 patients with MetS and 30 patients without MetS as control group. All entire coding exons of IRS-1 and IRS- 2 gene were amplified by PCR. Insulin resistance (IR) was estimated using the homeostasis model assessment (HOMA).

Results
In patients with MetS, 34 (34%) patients had G972R gene polymorphism and 36 (36%) had no nucleotide substitution at IRS-1 gene, 15 (15%) had G972R heterozygous, 7 (7%) had G972R homozygous, 2 (2%) had P1033P heterozygous/P1033P homozygous and 5 (5%) had P1033P heterozygous. In IRS-2 gene, 44 (44%) had no nucleotide substitution, 18 (18%) had G1057D heterozygous, 11 (11.0%) had G1057D homozygous, 2 (2%) had P1031P heterozygous/P1033P homozygous, 17 (17.0%) had P1033P heterozygous, 3 (3.0%) had P1033P homozygous and 5 (5%) had P1033P heterozygous/G1067D heterozygous polymorphisms in MetS (P = 0.0001). However, all of control had no nucleotide substitution in IRS-1 and IRS-2 genes. There were no statistically differences between patients who had gene polymorphism and not polymorphism in IRS-1 and IRS-2 for systolic and diastolic blood pressures, BMI, LDL- cholesterol, triglyceride, HOMA-IR, homocysteine, hsCRP and fibrinogen.

Conclusion
Insulin receptor substrat 1 and 2 genes polymorphisms were associated with metabolic syndrome but not cardiovascular risk factors such as blood pressure, BMI, cholesterol, triglyceride, HOMA-IR, homocysteine, hsCRP and fibrinogen levels.

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EP320
Changing expression of NOD-like receptors in GALT of rats at an experimental diabetes mellitus and pentoxifylline administration
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Introduction
Expression of NOD-like and NLRP receptors (PRR) is an innate immune response by the gut-associated lymphoid tissue (GALT) can play a critical role in an induction and progression of TIDM.

To study the peculiarities of NOD2 receptors in gut-associated lymphoid tissues (GALT) of rats with experimental STZ-induced diabetes mellitus and pentoxifylline (PTX) administration.

Methods
Researches were made on Wistar rats. For an induction of diabetes streptozotocin was used in doses 50 mg/kg. Structure of population of NOD2+ cells has been studied by the analysis of serial histological sections using the method of indirect immunofluorescense with monoclonal antibodies to NOD2 of rat.

Results
It has been established that diabetes development was accompanied with 37–45% (P < 0.05) increase in quantity of NOD2 cells on the 14th day, but by the 4th week of disease their number returned to the benchmarks. Induction of diabetes leads to increased in concentrations of NOD2 on 7–28% in macrophages and dendritic cells and a decrease on 8–12% in lymphocytes. PTX administration of diabetic animals reduces the quantity of NOD2+ cells on 29% (P < 0.05) in mucous membrane of villus 42% in subepithelial zone of ILF by the 14th day of experimental diabetes mellitus. But by the 4th week of disease their number returned to the benchmarks in mucous membrane of villus and in subepithelial zone of ILF it increase on 29%. The concentration of NOD2 also decreased in 2nd week of diabetes on 8–15% in NOD2+ macrophages and NOD2+ -dendritic cells.

Conclusions
The expression augmentation with NOD2 in ileum immunopositive cells can influence the differentiation of subsets of immunopositive cells and their proinflammatory cytokines production, thus acting as one of triggers of diabetes development and progression.
Introduction
Biochemical and clinical vitamin B12 deficiency has been demonstrated to be highly prevalent among patients with diabetes mellitus. The aims of the study were to: 1. compare the vitamin B12 (VB12) levels, and 2. to investigate the relationship between VB12, fasting insulin levels and HOMA-IR levels in elderly patients with metabolic syndrome (MetS).

Subjects and method
Study population included 121 (mean age 64.3 ± 14.1 years) (80 female, 41 male) elderly patients. Patients were evaluated for MetS by Adult Treatment Panel III (ATPIII). Data such as VB12, insulin and other tests were retrospectively searched. Vitamin B12 deficiency was defined as B12 concentrations <197 pg/ml.

Results
Metabolic syndrome was diagnosed in 39 elderly patients (%32.2). The prevalence of low VB12 was 45.8% in elderly with MS. Serum VB12 levels were significantly lower among patients aged ≥70 years (P<0.05). In elderly patients with MetS, mean levels of VB12, fasting insulin and HOMA were found to be 370.1 ± 58.6 pg/ml, 13.4 ± 1.1 μU/ml, 3.0 ± 0.1, respectively. However, mean levels of VB12, fasting insulin and HOMA were found to be 383.9 ± 66.0 pg/ml, 8.4 ± 2.7 μU/ml, 2.71 ± 0.9, in the other elderly patients, (P = 0.90), (P = 0.70), (P = 0.03), respectively. Mean levels of VB12 were negatively correlated with fasting insulin levels (r = -0.800, P = 0.01) in elderly with MetS.

Conclusion
Mean levels of VB12 were not different in elderly patients with or without MetS, but negatively correlated with fasting insulin in elderly with MetS.

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EP322
Does hepatitis C virus (HCV) infection has a role in the pathogenesis of diabetes mellitus in patients with β thalassemia

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Introduction
In patients with β thalassemia major (TM) The interplay between liver siderosis and hepatitis C virus (HCV) infection may facilitates the progression to insulin resistance (IR) and diabetes mellitus (DM).

Objectives
Many TM patients are infected with either HCV. Therefore, we aimed to explore if there is any association between DM and HCV-RNA positivity with different genotypes.

Patients and methods
148 TM patients (age range: 15–53 years; 72 males and 76 females), 78 were HCV-RNA positive. Fifteen patients (10.1%) had type 1 DM. The HCV genotype was done using specific primers in all thalassemic patients with DM as well as in 46 non diabetic TM patients. Serum HCV-RNA was detected using a sensitive polymerase chain reaction assay. We assessed also the frequency of DM in TM patients with HCV- and HCV-RNA-, and HCV+ and HCV-RNA-.

Results
The commonest genotype in TM patients with and without DM was 1b (Table 1). HCV genotype did not differ statistically between diabetic and non-diabetic thalassemic patients (χ² test). In addition the frequency of DM did not differ among TM patients with HCV+ and HCV-RNA-, and HCV+ and HCV-RNA-.

Table 1.

<table>
<thead>
<tr>
<th>HCV genotype</th>
<th>TM patients with diabetes</th>
<th>TM patients without diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>9 (60%)</td>
<td>27 (58.6%)</td>
</tr>
<tr>
<td>1b/2</td>
<td>0</td>
<td>1 (2.1%)</td>
</tr>
<tr>
<td>2</td>
<td>4 (26.6%)</td>
<td>14 (30.4%)</td>
</tr>
<tr>
<td>2a,2c</td>
<td>1 (6.6%)</td>
<td>2 (4.2%)</td>
</tr>
<tr>
<td>3a</td>
<td>1 (6.6%)</td>
<td>3 (6.6%)</td>
</tr>
</tbody>
</table>

Summary
Our study did not show statistically significant association between DM and HCV-RNA positivity, larger studies are required for acquiring better knowledge about the pathogenetic mechanisms that link HCV infection with abnormal glycemic abnormalities.

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EP323
Abstract withdrawn.

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EP324
The relationship between higher left ventricular mass index and plasma total homocysteine levels in patients with type 2 diabetes mellitus

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Purpose
The aim of the present study was left ventricular mass index (LVMI) in type 2 diabetes mellitus (T2DM) patients may be related increased circulating homocysteine (Hcy) levels.

Methods
The study group comprised 130 patients, and all patients were newly diagnosed with diabetes and were not taking any medication. Measures of left ventricular mass (LVM) were assessed using Devereux formula and left ventricular mass index (LVMI) was calculated as LVM divided by body surface area. Hcy levels were measured using high-performance liquid chromatography.

Results
Forty five patients (34.6%) of all patients with higher LVMI. In univariate logistic regression analyses age, creatinine and Hcy count all significantly associated with higher LVMI. When these three variables were included in a multivariate regression modeling Hcy levels were found to be significantly associated with the higher LVMI.

Conclusions
Hyperhomocysteinemia (Hhc) can be a predictor of in T2DM patients.

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EP325
Description of practices related to insulin injection therapy and sharp disposal among patients attending the diabetic clinic, Colombo North Teaching Hospital, Sri Lanka

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Introduction
Diabetic patients on insulin therapy are compelled to use sharps such as insulin needles and lancets on a regular basis. As a result thousands of used sharps and bloodstained materials are generated daily by them. While there is a huge concern over sharps disposal practices in healthcare settings, the sharps disposal practices of diabetic patients living at home has been poorly documented.

DOI: 10.1530/endoabs.37.EP325
Methodology
Randomly selected sample of 158 diabetic patients were obtained from the diabetic clinic, Colombo North Teaching Hospital. Data collected using an interviewer administered questionnaire and clinic records.

Results
Sample population was aged between 21 and 90. Mean age 60. Majority had used insulin for more than 1 year 131/158 (83%). Very few 5/158 (3%) used the insulin pen while majority used syringes to inject insulin. Only 10 (6%) regularly checked blood sugar using needles/lancets. Majority 132/158 (84%) injected insulin more than twice per day and ≥50% used the same needle more than six times, for more than 3 days. Majority 150/153 (98%) of the syringe users recapped the needle. A significant number 73/158 (46%) also involved others when injecting and disposing needles. Used needles/pen were disposed in to a common household garbage bin, sharps container, toilet pit, garbage dump and indiscriminately by 66 (42%), 9 (6%), 8 (5%), 14 (8%), 11 (7%), respectively. Some 15/158 (9.5%) have collected sharps since beginning without disposing. Many respondents had received no information on how to dispose of their sharps. Those who recalled receiving information were more likely to dispose of their sharps safely.

Conclusions
Insulin-dependent diabetic patients are not educated on safe sharps disposal methods, leading to unsafe disposal of needles. Appropriate education on the correct disposal of sharps should be an integral part of their diabetic counselling.

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EP326
Vaccination status and factors affecting vaccination among diabetics
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Vaccines are the most effective tools for preventing some infections. World Health Organization (WHO) and Ministry of Health (MoH) in Turkey recommends vaccination for people with diabetes. Our aim was to determine the prevalence of vaccination rates among diabetes in three different cities (Kutahya, Eskisehir and Malatya) in Turkey. 475 patients (307 female, 168 male) attending outpatient clinics for endocrinology were asked to fill in a questionnaire. The vaccination rates were very low. The rate being vaccinated was 27% for influenza. The vaccination rate for pneumococcus, tetanus and hepatitis B were 8%, 20, 6% and 16, 2, respectively. The vaccination rates among type 1 diabetes were higher than type 2 diabetics. Survey results indicated that leading factor negatively influencing vaccine uptake for influenza was that 25.9% of diabetics did not know that they are in risk for influenza and 5.3% do not believe that there may be a threat of influenza pandemic or epidemic. 6.1% did not want vaccination because of side effects. The reason for the lowest vaccination rate for pneumococcus vaccine may be dependent on the factor that this vaccine is not provided by health care providers, but the other vaccines are free for risk groups in Turkey. Also the pneumococcus vaccine is not well known among diabetics, because 60.6% of diabetics in our study population did not hear about the vaccine. 46.3% of diabetics reported that they did not know that there is a need of booster for tetanus immunization. Increased awareness of physicians may help improve vaccination rates against influenza, pneumococcal disease, tetanus and hepatitis B. Education programs for physicians and also diabetic patients may improve the vaccination rates in patients with diabetes.

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EP327
Prevalence of orthorexia in diabetic patients
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Introduction
Orthorexia (nervosa) is an eating disorder, characterised by an obsession with avoiding foods perceived to be unhealthy. Though it has not been recognised as a pathological entity in Diagnostic and Statistical Manual of Mental Disorders – IV yet, interest in the condition has increased recently. This study aimed to determine the prevalence and risk factors of orthorexia in a group of diabetic patients.

Methods and design
134 (63 female) diabetic patients who admitted to the outpatient clinic of our department were enrolled. Demographic information, educational status, diabetic history, care, and treatment, height, and weight of all cases were recorded. Ortho-15 Questionnaire was applied to all participants. Each patient can score minimum 15, maximum 60 points from this test. Those scoring 40 points and less are accepted to be orthorectic.

Results
The mean age of the group was 59.9 ± 11.7 years. The Ortho-15 test revealed that the minimum score was 25, and the maximum 46 points. No relation was determined between educational status, BMI and presence of orthorexia. 15.5% of males and 11.1% of females were found to be orthorectic (P > 0.05). The mean duration of diabetes of the whole group was 10.1 ± 8.8 years and there was no relation between duration of diabetes and presence of orthorexia.

Conclusion
This study revealed that orthorexia was not frequent in this group of patients. Performing the test on larger groups making comparisons, may introduce different results.

DOI: 10.1530/endobs.37.EP327

EP328
Metabolic control in patients with type 1 diabetes mellitus associated with depression
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Objective
The assessment of glycemic control and concentration of lipids in the blood in patients with type 1 diabetes mellitus (DM-1), depending on the presence of depression (DP).

Methods
There were examined 163 patients with DM-1. To assess severity of DP there was used Hospital Anxiety and Depression Scale (HADS). There were determined the level of fasting blood glucose (BG), BG level in 2 hours after a meal, the average daily BG level for 3 days and HbA1c level. Also there were determined the total amount of cholesterol (TC), triglycerides (TG), HDL cholesterol (HDLC). The amount of HDL cholesterol (LDLC) and the amount of very LDL cholesterol (VLDLC) were determined by calculation.

Results
Increased level of HbA1C was found in patients with DP, the mean daily glucose compared with patients without DP (9.70% vs 8.40%, P < 0.001; 9.02 mmol/l vs 8.10 mmol/l, P = 0.03 respectively). There has been established a positive correlational relationship between the level of DP according to the HADS scale and the level of daily mean BG (r = 0.22, P < 0.05). Development of DP at DM-1 is associated with the level of HbA1C 7.5% or more (OR = 0.89; P = 0.03; 95% CI 0.30–1.48). The results of evaluation of biochemical parameters characterizing lipid metabolism according to the presence of DP indicate, that the level of TC in patients with DP was higher than in patients without DP (5.10 mmol/l vs 4.80 mmol/l, P = 0.04). There has also been determined that the level of LDLC was 3.10 mmol/l in patients with DP vs 2.65 mmol/l in patients without DP and exceeded by 14.5% the value of comparison group (P = 0.05).

Conclusions
The risk of development of DP in DM-1 is associated with decomposition of carbohydrate metabolism and dyslipidaemia.

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EP329
Trends in diabetic ketoacidosis presentations at a major rural referral centre in Australia
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Aim
To study trends in presentation and management of diabetic ketoacidosis (DKA) at a rural referral centre, to ultimately assist with development of a formal management protocol.
Clinical characteristics in patients with type 2 diabetes mellitus: a cohort study
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Objective
To assess metabolic control, cardiovascular risk factors and treatments in type 2 diabetes mellitus (T2DM) patients.

Methods
Observational and cross-sectional study of 238 T2DM patients who visited endocrinology clinics for the first time or those who did not undergo periodic revisions during the previous year of the study. All reported patients were transferred from outlying facilities. These factors need to be considered when planning service delivery and have been considered when developing a formal protocol appropriate for a major rural referral centre.

Results
Out of 103 examinees, 66 (64.1%) suffer from STEMI. Mean age of study population is 67 ± 9 years, 59 (57%) are males. Mean T2DM duration is 7 (1–30) months and it influences on duration of hospital stay (p = 0.232, P < 0.05), but not on clinical outcome (p = 0.174, P > 0.05). Mean duration of hospital stay is 8 and 5.5 days in STEMI and NSTEMI patients respectively, with no difference between groups (log rank χ² = 0.476, P > 0.05). HbA1C values influence on duration of hospital stay (p = 0.213, P < 0.05), opposite to admission glycaemia (p = 0.148, P > 0.05). Out of four patients (3.9%), who passed away, three suffered from STEMI. Neither admission glycaemia (p = 0.165, P > 0.05) nor HbA1C values (p = 0.047, P > 0.05) do not have effect on clinical outcome.

Discussion and conclusion
In present study, admission glycaemia do not influence either on duration of hospital stay or clinical outcome. Diabetes duration and HbA1C values extend mean duration of hospital stay, but do not influence on clinical outcome.
**EP333**

**Variability of anthropometric, echocardiographic and biochemical indices with comorbid pathology – essential hypertension and type 2 diabetes**

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The mechanisms of development and progression of essential hypertension (EH) and concomitant type 2 diabetes (DM2) still remain not completely studied, so the comprehensive evaluation of the contribution of various indicators to the formation of this comorbidity have scientific interest.

The aim of the study was comprehensive assessment of the variability of anthropometric, echocardiographic and biochemical parameters in patients with EH and concomitant DM2. We examined 241 patients aged 45–60 years. The main group consisted of 153 patients with EH stage II, grade 2 and DM2 moderate, subcompensated; comparison group – 70 patients with EH stage II, grade 2 without DM2. The control group consisted of 20 healthy individuals.

Integrated data processing was carried out with the help of factor analysis using principal component. In the analysis there were 73 variables, based on the relationships among which there were four factors that together explain 52.61% of the total variability of the empirical data. In this case the first and the most powerful factor explained 33.07% of the total variability of indices. The highest load of Factor 1 were at indicators diastolic hypertension, malondialdehyde, tumor necrosis factor-α, interleukin-6, blood glucose, insulin, HbA1c, HOMA, leptin, intima-media thickness of the common carotid artery, while at the negative pole of this factor were superoxide dismutase, catalase, endothelium-dependent vasodilation, adiponectin, LDL.

Averaged factor estimates for Factor 1 were: 0.517±0.025 – in the main group, 0.986±0.039 – in the comparison group and -2.476±0.037 – in the control group with highly significant differences between the factor scores in all groups (P<0.001).

Conclusion

We discovered four main factors, the general action of which explained 52.61% of variability indices in comorbid pathology – EH and DM2. Factor assessment of the most powerful Factor 1 with high significance made the studied groups of patients differ from each other.

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**EP334**

**Salt addition and the risk of type 2 diabetes mellitus: a case–control study**

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Introduction

Type 2 diabetes appears to involve interaction between susceptible genetic backgrounds and environmental factors. It is important to identify modifiable risk factors that may help reduce the risk of type 2 diabetes. Data on salt intake and the risk of type 2 diabetes are limited. The aim of the study was to assess the relationship between adding salt to prepared meal and the risk of type 2 diabetes mellitus.

Methods

A case–control study included 234 cases with a newly confirmed diagnosis of type 2 diabetes mellitus during the one whole year and 468 controls which were free of the disease. Cases and controls (ratio 1:2) were matched by gender and age (±5 years). A specifically designed questionnaire was used to collect information on possible risk factors of type 2 diabetes. Anthropometrical measurements were made according to World Health Organization recommendations. The odds ratios (OR), and 95% CI for type 2 diabetes were calculated by a conditional logistic regression.

Results

The cases had higher BMI and significantly lower education level, compared to the controls. Variables such as family history of diabetes, education, BMI, waist circumference, morning exercise, eating speed, cigarette smoking, arterial hypertension, plasma triglycerides, occupational and marital statuses were retained in the models as confounders because their inclusion changed the value of the OR by more than 5% in any exposure category. After adjusting for possible confounders about two-fold increased risk of type 2 diabetes mellitus was determined in those subjects whose adding salt to prepared meal when it is not enough or almost every time without tasting (1.82; 95% CI 1.19–2.78; P=0.006) vs subjects whose never adding salt to prepared meal.

Conclusion

Our data support a possible relationship between adding salt to prepared meal and the increased risk of type 2 diabetes mellitus.

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**EP335**

**Relationship between adiponectin and anthropometric parameters, insulin resistance and transaminase levels in patients with nonalcoholic fatty liver disease and type 2 diabetes**

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The basis of the pathogenesis of nonalcoholic fatty liver disease (NAFLD) is insulin resistance (IR) which appears on the background of abdominal obesity (AO) which, in turn, is a key factor in the emergence of an imbalance between adipokines entailing a disturbance of lipid and carbohydrate metabolism, which ultimately leads to the damage of the liver cells, the development of inflammation, fibrosis and apoptosis. The goal – to study features of changes in the level of adiponectin (AN), depending on the function of the liver and IR index in patients with NAFLD and type 2 diabetes mellitus (T2DM) and AO.

Methods

25 patients with NAFLD and T2DM (HbA1c <7.5%) and control group (n=10) underwent clinical examination including assessment of BMI, waist circumference (WC), liver function (transaminases – ALT, AST) and index HOMA-IR.

Results

The changes in BMI were observed in 94.5% of patients, including obesity 1st degree – in 54.6%, 2nd degree – in 31.4 and 4.6% – obesity 3rd degree. AN level was reduced compared to control (8.7±2.4 ng/ml vs 18.4±2.1 ng/ml, P<0.05) and correlated with the degree of obesity – 6.5±2.1 ng/ml in patients with grade 3 obesity (P<0.05). There was a negative relationship between the level of AN and BMI (r=-0.36; P<0.01), WC (r=-0.34; P<0.05). The level of AN significantly decreased with increasing levels of ALT (r=-0.44; P<0.001) and AST (r=-0.46; P<0.001). An inverse relationship between the level of AN and the index HOMA-IR was determined (r=-0.46; P<0.001).

Conclusions

Hypoadiponectinemia in patients with NAFLD and T2DM is associated with AO, the deterioration of the liver function and progression of IR that contributes to the further development of metabolic abnormalities in the liver.

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EP336 Diabetic gallbladder, dyspepsia and metabolic effects
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The purpose of the study was to determine the functional state of the gallbladder (GB) in patients with type 2 diabetes mellitus (T2DM) in combination with metabolic syndrome (MS).

Methods
40 patients with T2DM and obesity of I–II degree were examined as well as 20 healthy volunteers. Ultrasonography, dynamic echoholecystography and duodenal intubation were performed. The motor function of GB was assessed by emptying coefficient (Kempt = \( V_0 / V_0 \times 100\% \)) and the index of contractility (IC = \( V_{\max} / V_{\max} \)). Lipid and carbohydrate metabolism was assessed.

Results
The following signs of GB hypotension were revealed: increase of GB initial volume to 80.2 ± 1.1 cm³ (in the control group − 25.9 ± 1.9 cm³) (\( P < 0.05 \)); increase of GB hypokinesia – reduced Kempt of GB on 30th minute of volume to 80.2

EP337 Tumour necrosis factor-\( \alpha \) and insulin resistance in patients with nonalcoholic fatty liver disease in combination with type 2 diabetes mellitus
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Tumour necrosis factor-\( \alpha \) (TNF-\( \alpha \)) impairs liver function and contributes to the pathogenesis of nonalcoholic fatty liver disease (NAFLD) in patients with type 2 diabetes mellitus (DM-2) with different trophological status.

Purpose
To assess the relationship between the level of TNF-\( \alpha \) and indices of carbohydrate metabolism in patients with NAFLD and its combination with DM-2 with different trophological status.

Methods
90 patients with isolated NAFLD and in combination with DM-2 with normal metabolite status.

Results
TNF-\( \alpha \) was significantly (\( P < 0.001 \)) increased in all groups as compared to the controls (24.2 ± 1.06 pg/ml), the level was the highest in group 3 (96.6 ± 0.72 pg/ml) and was significantly different from that in groups 1 and 2 (66.2 ± 1.07 pg/ml and 86.4 ± 1.21 pg/ml, respectively). In groups 1 and 2 the correlation was established between TNF-\( \alpha \) and IRI (\( r = 0.33, P < 0.05 \) and \( r = 0.37, P < 0.05 \), respectively). In group 3 the significant correlation was established between the level of TNF-\( \alpha \) and fasting blood glucose (\( r = 0.46, P < 0.05 \), IRI (\( r = 0.78, P < 0.05 \)) and HOMA-IR (\( r = 0.64; P < 0.05 \)).

Conclusion
The correlation between TNF-\( \alpha \) and indices of carbohydrate metabolism is connected with the ability of TNF-\( \alpha \) to enhance the carbohydrate metabolism, insulin resistance, and support the role of TNF-\( \alpha \) in pathogenesis of NAFLD, namely, in damage of hepatic gluconeogenesis, especially in patients with associated DM-2 and obesity. In addition, isolated NAFLD can independently cause the metabolic consequences.

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EP338 Pancreatogenic diabetes
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Aims
Diabetes mellitus secondary to pancreatic disease and pancreatic surgery (pancreatogenic; type 3c) is a discrete entity to common types of diabetes and there are no well established guidelines for its management. At Nottingham University Hospitals, we have set up a multidisciplinary pancreatogenic diabetes clinic since 2008. The aim of this study is to look at the outcome of the clinic since it’s been established.

Methods
Case notes and hospital database of all 51 patients (32 male, 19 female) attending the clinic between 2008 and April 2014 were reviewed retrospectively. Their mean duration of diabetes was 5 ± 0.76 years.

Results
Mean HbA1c on first attendance was 70.4 (s.d. 21.6) and at 1 year it was 68.1 (s.d. 21.2). Mean weight at 1 year showed an increase from 75.2 ± 3.1 kg to 83 ± 4.1 kg. BMI increased from 26.0 to 29.8 kg/m². During the first year in the clinic, 15 patients had their medications reviewed and changed and there were only four patients admitted; three had problem with glycaemic control with DRA and one had multiple admissions due to hypoglycaemia.

Conclusions
There was improvement in HbA1c of the patients at 1 year. Mean BMI showed that patients were initially overweight and their BMIs have increased at 1 year. Attendance rates at the clinic are generally good; 80% of appointments have been attended. This showed that there is positive outcome of the pancreatogenic diabetes clinic. Therefore, patients with pancreatogenic diabetes should be managed in such clinic rather than usual diabetes clinics.

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EP339 Vitamin D level in impaired fasting glucose and impaired glucose tolerance (prediabetic) patients
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Introduction
Impaired fasting glucose (IFG) is defined as being present in those whose fasting blood glucose level is consistently elevated above normal, but is not high enough to be considered as having diabetes mellitus. Impaired glucose tolerance (IGT) is defined as being present in those whose second hour plasma glucose level is higher than normal, but is not high enough to be considered as having diabetes mellitus. Low serum 25-hydroxyvitamin D levels are associated with glucose intolerance, diabetes mellitus, and metabolic syndrome. To date, the literature is conflicting regarding the relationship between vitamin D levels and prediabetes. Our aims in this study were to evaluate serum 25-hydroxyvitamin D levels and their association with prediabetic metabolic patterns.

Material and methods
Participants were 220 patients from our endocrine clinic: 85 with isolated IFG, 50 with isolated IGT, 85 with both IFG and IGT, and 80 normoglycaemic healthy subjects with similar age, gender, and BMI. A detailed history and physical examination of the patients were performed. 25-hydroxyvitamin D, calcium, phosphorus, albumin and PTH levels were measured. 25-hydroxyvitamin D levels were categorised as adequate if > 30 ng/ml, insufficient if 20–30 ng/ml, and deficient if < 20 ng/ml.

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Results
We found significantly lower 25-hydroxyvitamin D levels in the IGT (11.7 ± 6.5 ng/ml) (P < 0.007) and IFG + IGT patients (13.2 ± 7.2 ng/ml) compared to controls (16.6 ± 9.8 ng/ml) (P = 0.047). Lower 25-hydroxy vitamin D levels were associated with a higher risk of IGT (OR 2.57, 95% CI 1.01–6.53, P = 0.043). 25-hydroxyvitamin D levels were similar in the control group and IFG group. Significant differences in 25-hydroxyvitamin D levels between the IFG group, IGT group and IFG + IGT group were not found.

Conclusion
Vitamin D insufficiency and deficiency are associated with IFG, IGT, and combined IFG and IGT. However, the only statistically significant association was that between 25-hydroxyvitamin D levels and IGT.

Disclosure
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**EP340**

Effects of H. pylori eradication on metabolism and body weight in obese and non-obese patients

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Introduction
Many studies showed that H. pylori infection could be an independent predictor for insulin resistance and could regulate metabolism and body weight.

Aim
To evaluate changes in metabolism induced by an oral glucose tolerance test (OGTT) before and after antibiotic eradication treatment in patients colonized by H. pylori.

Materials and method
Prospective case-controlled study with a sample of patients colonized by H. pylori. In an intra-subject analysis, clinical data and levels of ghrelin and GLP1 were analysed at baseline and post-OGTT before and after antibiotic eradication treatment.

Results
We studied 32 patients (75% women and 21.9% obese). Average age was 49 ± 11.5 and 46.9% had personal history of gastrointestinal disease. We found a significant decrease of HbA1c and 120 post OGTT glucose after treatment; and significant correlations between ghrelin with waist circumference and BMI (negative), and with glucose, insulin, HbA1c and LDL-Chol (positive). We also found significant positive correlations between GLP-1 and insulin, and between HbA1c and glucose, insulin, HbA1c and LDL-Chol (positive). We also found significant differences in levels of ghrelin and GLP1 post-treatment in obese and non-obese patients

Conclusions
H. pylori.

Significant differences in levels of ghrelin and GLP1 were found after eradication. Significant correlations between plasma glucose and insulin with ghrelin and GLP1 were found. More than 85% of patients achieved H. pylori eradication.


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**EP341**

Discrepancies between the glycosylated haemoglobin based criteria and glucose based criteria for diagnosis of diabetes and pre-diabetes

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**Objectives**
The number of people with diabetes is increasing globally; hence necessitate identifying diabetes earlier and more efficiently. Recently, American Diabetes Association (ADA) recommended the use of glycated haemoglobin (HbA1c) as an alternative to glucose based criteria for diagnosing type 2 diabetes and pre-diabetes. Hence, we aimed to evaluate the discrepancies between HbA1c- and glucose-based criteria for diagnosis of diabetes and pre-diabetes in Nepalese population.

**Methods**
A total of 2502 subjects aged 30 years or older, who attended university hospital and subjected for measurement of HbA1c, fasting plasma glucose (FPG) and 2-hour plasma glucose (PGP) level were recruited in the study. Newly diagnosed diabetes and pre-diabetes were defined by ADA-glucose based and ADA- HbA1c criteria. Statistical analyses were performed using SPSS software to evaluate discrepancies.

**Results**
The percentages of newly diagnosed individuals with diabetes were 12.87% (322/2502) using the FPG criterion alone, 12.07% (302/2502) using the PPG criterion alone, 14.55% (364/2502) using the HbA1c criterion alone and 10.51% (263/2502) using FPG, PPG & HbA1c criteria in combination. Significant discordance occurred for 3.28% (82/2502) with HbA1c- and glucose-based criteria and for 1.68% (42/2502) with HbA1c- and FPG-criteria. Among the study subjects, 2.86% of individuals with a FPG and 2.12% of individuals with HbA1c were found to be pre-diabetes.

**Conclusions**
Significant discordance exists between the HbA1c- and glucose-based diagnostic criteria for diagnosis of diabetes and pre-diabetes in Nepalese population. Hence, we concluded that using glucose based criteria merely may result in an underestimation of diabetes and pre-diabetes.

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**EP342**

Familial partial lipodystrophy linked to a novel peroxisome proliferator activator receptor-γ mutation, H449L

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Introduction
Familial partial lipodystrophy (FPL) is a rare genetic disorder characterised by a selective lack of subcutaneous fat that is associated with insulin resistance and diabetes. FPL has been reported to be caused by mutations in the peroxisome proliferator activator receptor-γ (PPARG) gene, which encodes a key transcription factor that regulates adipocyte differentiation and insulin sensitivity.

Material and methods
The objective of this study was i) to describe the phenotype associated with a novel heterozygous missense PPARG mutation, H449L, discovered in a Turkish family; and ii) to compare the fat distribution and metabolic characteristics of subjects with the PPARG H449L mutation to that of a cluster of FPL patients with various LMNA mutations (n = 4) to that of a cluster of FPL patients with various LMNA mutations (n = 4) to that of a cluster of FPL patients with various LMNA mutations (n = 4) to that of a cluster of FPL patients with various LMNA mutations (n = 4) to the four mutation carriers were overtly diabetic or had impaired glucose tolerance. Pioglitazone therapy in these three individuals resulted in a modest improvement in their metabolic control, and regular menstrual cycles in both females.

Conclusions
We suggest that relatively modest fat loss in patients with PPARG mutations may render the recognition of the syndrome more difficult in routine clinical practice.
Irisin (Ir), a recently identified adipokine, cleaved and secreted to the circulation from the FNDC5 protein in response to physical activity and some environmental conditions has been postulated to induce the differentiation of a subset of white adipocytes into brown fat and mediates the beneficial effects of exercise on metabolic homeostasis. Polycystic ovary syndrome (PCOS) – one of the most frequent endocrinopathies affecting women of child-bearing age is associated with reproductive problems and also metabolic alterations leading to obesity and obesity-related diseases. It is commonly accepted that obesity-associated disorders are related to the type of fat distribution. Individuals with excess of visceral (android) fat but with normal BMI, called MONW (metabolically obese but normal weight), are burdened with obesity-related disease. The aim of our study was to evaluate the relationship between Ir plasma concentrations in PCOS patients and healthy control group in the context of adipose tissue deposits. Our study group consisted of 179 patients with PCOS and a population of 122 healthy control group (both groups aged 25–35 years). We isolated a MONW patients using DEXA criteria of depA (android fat deposit, >30.2% and BMI <25) for the Polish population. In the MONW patients we observed a negative correlation with Ir concentration. We found a statistically significant positive association between Ir concentration and type of adipose tissue deposit – (depA) in the whole study group (P = 0.006) and in the control group (P = 0.00); while in the PCOS a negative correlation between depA and Ir group (P = 0.00) was shown. Our data revealed for the first time that Ir concentration is connected with type of body fat distribution. In this respect PCOS differs from healthy subjects. Moreover we confirmed that an increased Ir secretion in obesity could result from an adaptive response or Ir-resistance.

EP344

The GH treatment results in the increase of irisin concentration in plasma

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Brown adipose tissue metabolism is of remarkable pathophysiological interest, because it could be a target for future therapies for obesity and metabolic syndrome. Irisin (Ir), recently identified novel adipokine is essential in a white-to-brown fatty tissue transdifferentiation, and mediates some of the positive influences on metabolic disorders through increase of energy expenditure. The exact regulation of Ir secretion and action is unknown but significant positive associations of circulating Ir with GHs and IGF1 were found. We studied Ir response in a group of patients treated with supraphysiologic doses of GH (rGH). The study group consisted of 35 Turner syndrome (TS) patients aged 3.2–16.07 years (mean 8.2 years) diagnosed by karyotyping. The rGH was applied in a dose 0.05 mg/kg per day Prior to and following the treatment (mean 1.47±0.89 years) anthropometrical data were recorded as well as biochemical parameters were measured: Ir, OGTT, insulin,IGF1, and IGFBP3. The increase of IGF1 concentration at the end of observation was significant (from 119.4±62.46 to 413.7±204.38 ng/ml, mean ±s.e., P = 0.000); the significant rise of Ir level was recorded on rGH treatment (2.1±1.03 vs 2.47±0.79 μg/ml, mean ±s.e., P = 0.035). The rGH treatment increased insulin resistance revealed by increased HOMA values (median 0.64±0.45 before and 0.92±0.97 after, P = 0.02). The correlation between Ir and IGF1 levels was not significant neither before nor on the treatment (P = 0.22 and P = 0.95 respectively). The correlation between Ir and insulin (r = 0.44, P = 0.01) and Ir and HOMA (r = 0.46, P = 0.007) was significant. Result of the study showed an increase in Ir level following GH application. It seems to be not IGF1 mediated. Ir may mediate some metabolic effects of GH treatment. We are unable to conclude whether Ir rise is connected with direct GH stimulation, their influence of body composition, or with altered insulin sensitivity.

EP345

Acquired partial lipodystrophy is associated with increased risk for metabolic complications

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Objective

Acquired partial lipodystrophy (APL) is a rare disorder characterized by progressive selective fat loss. In previous studies, metabolic complications were reported to be relatively rare in APL, while they were quite common in other types of lipodystrophy syndromes. However, so far, there has been no systematic study on metabolic complications in APL.

Methods

We have systematically evaluated 21 APL patients in the Turkish Lipodystrophy Study Group (TuLip) registry who were enrolled in a prospective follow-up protocol. Patients with congenital generalized lipodystrophy (CGL), type 1 diabetes, type 2 diabetes and healthy controls were included for comparison. Subjects were investigated for metabolic abnormalities. Fat distribution was assessed by whole body MRI. Hepatic steatosis was evaluated by ultrasound, MRI and MR spectroscopy. Patients with diabetes underwent a mix meal stimulated C-peptide/insulin test to investigate pancreatic β cell functions. Leptin and adiponectin levels were measured.

Results

Fifteen individuals (71.4%) had at least one metabolic abnormality. Six patients (28.6%) had diabetes, 12 (57.1%) hypertriglyceridemia, 10 (47.6%) low HDL, and 11 (52.4%) hepatic steatosis. Steatohepatitis was further confirmed in two patients with liver biopsy. Anti GAD was negative in all APL patients with diabetes. Their leptin and adiponectin levels were decreased compared to patients with type 2 diabetes and controls. However, consistently very low leptin levels as detected in patients with CGL, was not the case. The mix meal test suggested that APL patients with diabetes had a significant amount of pancreatic β cells functioning, and their diabetes was apparently associated with insulin resistance.

Conclusions

Our results reveal that most patients with APL develop metabolic abnormalities associated with insulin resistance. Further research is needed to clarify if they would benefit from metreleptin treatment.

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EP346
Association between +276 G>T polymorphism of the adiponectin gene (ADIPOQ) and insulin resistance in Ukrainian patients with type 2 diabetes mellitus (T2DM)
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Variants of ADIPOQ have been inconsistently associated with adiponectin level in diverse populations. We explored association of single nucleotide polymorphism (SNP) +276 G>T (rs1501299) with circulating total adiponectin and insulin resistance (IR) in Ukrainian T2DM cohort.

Materials and methods
544 T2DM patients (M/F: 241/303, age 56±3.4 years, diabetes duration 7.8±1.0 years, BMI 31.7±0.2 kg/m², HbA1c 7.6±0.2%) and 215 healthy controls (C) were genotyped. The SNP +276 G>T in the ADIPOQ was detected using PCR-RELP. Plasma total adiponectin, IR and lipid profile were determined. Statistical analysis was performed with ANOVA and χ² test.

Results
Comparing with C significant (P<0.001) increase in triglyceridaemia (2.99±0.12 vs 1.23±0.26 mM), plasma FFA levels (1.35±0.03 vs 0.34±0.07 mM), plasma insulin levels (31.24±7.11 vs 85.21±8.01 PM) and HOMA-IR (8.35±0.40 vs 1.77±0.41) as well as hyperadiponectinaemia (4.99±1.61 vs 11.80±1.45 mg/l) were observed in T2DM patients. Major allele in the studied groups was G (frequency in C: 0.991, and in diabetics: 0.009). In T2DM the T allele frequency was 0.399 and different significantly from C (P<0.037). In comparison with C, T2DM had more TG (16.9% vs 9.3%, P<0.05), but less GG (37.1% vs 47.4%, P<0.05) homozygotes. It was determined lower severity of dyslipidemia, i.e. total cholesterol (P<0.01), triglycerides (P<0.02) and β-lipoprotein cholesterol (P<0.05) against the background of less hyperadiponectinaemia (on 15.4%) in GG homozygotes (P<0.01) compared to TT carriers. Higher HOMA-IR was revealed in TT compared to other genotypes with maximal difference in patients with obesity (HOMA-IR index in carriers of TT, GT and GG genotypes were 10.96±1.52, 8.40±0.65 and 8.96±0.74, respectively, P<0.02 for TT vs GT and GG).

Conclusions
The study demonstrates for the first time that ADIPOQ variants are associated with IR phenotype in Ukrainian T2DM patients. We suggest the predominant impact of metabolic disturbances and hyperinsulinaemia on diabetic hyperadiponectinaemia genesis.

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EP347
Vitamin D level in diabetic retinopathy
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Purpose
To determine the relationship between grade of diabetic retinopathy and serum vitamin D levels in diabetic patients.

Materials and methods
A total of 173 diabetic patients consisting of patients without retinopathy (n=67), patients with non proliferative diabetic retinopathy (NPDRP group n=47), patients with proliferative diabetic retinopathy (PDRP group n=59) was included in the study. Age and sex matched 55 healthy subjects was taken as a control group. Patients with type 1 DM, those taking vitamin D, multivitamine including vitamin D, drug affecting vitamin D metabolism like rifampin, phenytoine was excluded from the study. Patients with chronic renal failure was also excluded. Bilateral fundoscopic examination of all subject was done and serum creatinine, HbA1c, 25 hydroxy vitamin D (25 (OH)D) level of all subject were measured between May 2012 and September 2012.

Result
There was no statistical difference in age, sex, systolic tension, diastolic tension and BMI between groups. Serum creatinine level was also not statistically different between groups (P=0.11). The mean 25 (OH)D levels of PDRP group, NPDRP group, diabetic patients without retinopathy and control group was 11.9±6.4, 18.8±10.2, 16.6±7.5 and 20.1±9.2 ng/ml respectively. There was statistically significant difference between DPPD group and other groups in univariate analysis (P<0.001). When comparing 173 diabetic patients, regardless of retinopathy, with control group, 25 (OH)D levels was significantly lower in diabetic patients than control group (P=0.004).

Conclusion
Diabetic patients especially, patients with proliferative diabetic retinopathy had lower serum vitamin D level than healthy subjects. Additionally randomised, controlled, prospective studies are necessary to determine whether vitamin D treatment will stop or slow the progression of diabetic retinopathy in diabetic patients.

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EP348
Abnormalities in glucose metabolism are present in HCV/HIV co-infected patients with severe liver fibrosis even in the absence of diabetes
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Rationale
Type 2 diabetes mellitus (T2DM) is a well known independent prognosis factor associated with cirrhosis. Nevertheless, few studies are focused on the association between glucose metabolism and liver fibrosis in HCV/HIV patients and their conclusions are contradictory. The aim of our study was to investigate the relationship between glucose homeostasis and liver fibrosis in these patients.

Methods
In a cross-sectional study, we compared prevalence of glucose disorders and data related to its homeostasis according to degree of liver fibrosis. Liver stiffness was measured using transient elastography. Severe liver fibrosis was defined as liver stiffness ≥ 14 kPa. Insulin resistance was defined as a level of homeostasis model for assessment (HOMA-IR) ≥ 2.

Results
65 HCV/HIV co-infected patients were included. Prevalence of prediabetes and T2DM was higher (40 and 24%, respectively) among patients with severe fibrosis as compared to 37 and 3.7% among those with less severe degree of fibrosis (P=0.005). Among parameters related to glucose metabolism, levels of fasting glucose, HbA1c and HOMA-IR were significantly higher in patients with severe fibrosis (P=0.006, P=0.048 and P=0.001 respectively). Also, there was a positive correlation between HOMA-IR and liver fibrosis (r²=0.5, P<0.001).

When patients with T2DM were excluded, levels of fasting plasma insulin, HOMA-IR and the prevalence of insulin-resistance, were significantly higher among those with severe fibrosis (P=0.004, P=0.003 and P=0.049, respectively) and the positive correlation between HOMA-IR and liver fibrosis remained significantly present (r²=0.45, P<0.001).

Conclusions
Our data support that hyperinsulunism and insulin-resistance are frequently observed in HCV/HIV co-infected patients with severe liver fibrosis even in absence of overt T2DM. Detection of a high degree of liver fibrosis in HCV/HIV co-infected patients is another reason to optimize glycemic control in this population.

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EP349
Gamma glutamyl transferase and C-reactive protein in type 2 Saudi diabetic patients in relation to management modality and components of metabolic syndrome
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Rationale
Type 2 diabetes mellitus (T2DM) is a well known independent prognosis factor associated with cirrhosis. Nevertheless, few studies are focused on the association between glucose metabolism and liver fibrosis in HCV/HIV patients and their conclusions are contradictory. The aim of our study was to investigate the relationship between glucose homeostasis and liver fibrosis in these patients.

Methods
In a cross-sectional study, we compared prevalence of glucose disorders and data related to its homeostasis according to degree of liver fibrosis. Liver stiffness was measured using transient elastography. Severe liver fibrosis was defined as liver stiffness ≥ 14 kPa. Insulin resistance was defined as a level of homeostasis model for assessment (HOMA-IR) ≥ 2.

Results
65 HCV/HIV co-infected patients were included. Prevalence of prediabetes and T2DM was higher (40 and 24%, respectively) among patients with severe fibrosis as compared to 37 and 3.7% among those with less severe degree of fibrosis (P=0.005). Among parameters related to glucose metabolism, levels of fasting glucose, HbA1c and HOMA-IR were significantly higher in patients with severe fibrosis (P=0.006, P=0.048 and P=0.001 respectively). Also, there was a positive correlation between HOMA-IR and liver fibrosis (r²=0.5, P<0.001).

When patients with T2DM were excluded, levels of fasting plasma insulin, HOMA-IR and the prevalence of insulin-resistance, were significantly higher among those with severe fibrosis (P=0.004, P=0.003 and P=0.049, respectively) and the positive correlation between HOMA-IR and liver fibrosis remained significantly present (r²=0.45, P<0.001).

Conclusions
Our data support that hyperinsulunism and insulin-resistance are frequently observed in HCV/HIV co-infected patients with severe liver fibrosis even in absence of overt T2DM. Detection of a high degree of liver fibrosis in HCV/HIV co-infected patients is another reason to optimize glycemic control in this population.

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EP351
Insulin-induced lipohypertrophy diagnostics in diabetic patients: subcutaneous fat ultrasonography
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Introduction
Lipohypertrophy (LIH) is a chronic complication of diabetes mellitus that caused by frequent s.c. injections of insulin. Nowadays, LIH 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 compare the frequency of insulin induced LIH in diabetic patients revealed by ultrasonography of subcutaneous fat with those founded by palpatory method. This study was done on 215 diabetic patients (142 females and 73 males, mean age 46 years) who had been under the treatment with insulin a mean 10 years. Observation and palpation techniques, as well as ultrasonography of subcutaneous fat were used in assessing LIH in these diabetics.

Evaluation of subcutaneous fat was made in typical injection sites: paraumbilical and buttocks regions, lateral surfaces of hips and shoulders. All patients injected insulin in physiological regimen.

Results
On the basis of palpation LIH were revealed in 66 patients (30.7%), while pathologic areas of subcutaneous fat didn’t discover in 149 subjects (69.3%). Further ultrasonography of injection sites was performed to all patients. LIH were revealed in 186 patients (86.5%), including those 66 subjects with palpatory changes. Pathologic areas of subcutaneous fat the most often were occurred in paraumbilical regions – 131 patients (61%). Also LIH were found simultaneously in two sites: paraumbilical regions and lateral surface of hips – 32 subjects (15%); paraumbilical regions and lateral surface of shoulders – 24 patients (11%).

Conclusions
LIH were modified due to good quality modern insulin and expansion their concentration. As a result, pathologic areas of subcutaneous fat were revealed in 30.7% patients by palpation, while LIH were found in 86.5% subjects by ultrasonography. Ultrasonography of subcutaneous fat could be used to diagnose LIH in diabetic patients in clinical daily practice.

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EP350
The prevalence of metabolic syndrome in patients with diagnosed type 2 diabetes
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Background and aims
The identification of metabolic syndrome (MS) is important for the appropriate management of associated cardiovascular risk factors. There are different criteria for the diagnosis of the metabolic syndrome proposed by the WHO and the National Cholesterol Education Program 2001 – NCEP/ATP III. The aim of our study was to determine the prevalence of the MS as the NCEP/ATP III criteria in a selected population of type 2 diabetes.

Patients and methods
We randomly selected 500 patients with T2 diabetes in Tirana district. 321/500 (64.2%) responded. 158 (49.2%) males. All the patients had completed anthropometric measures and lipid profile after an 8-h fast. The patients having two more criteria except diabetes, were defined as having MS.

Results
The prevalence of the MS was 64.5%, males 56.8% and females 75.7%. The prevalence increased with age, from 16% before 40 years of age to 78% at 70 years. Diabetes duration was not different in patients with or without MS (M: 6.7±3.4 vs 6.9±3.7; F: 7.2±3.8 vs 6.8±3.6 years). The number of components of the MS was related to the age (ANOVA P<0.05) but not to diabetes duration. Central obesity was present to males 36% females 85.4%, HTA 49.6 with the general Albanian population (64.5 vs 32%).

Conclusions
The results show that MS is two-fold more prevalent in type 2 diabetes, compared with the general Albanian population (64.5 vs 32%). The levels of cardiovascular risk factors are increased in type 2 diabetics and urged immediate efforts directed at controlling the components of MS (mainly obesity, physical inactivity and lipid control).

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EP352
Unvisible lipohypertrophy and diabetes compensation: is there link?
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Introduction
Lipohypertrophy (LIH) is a chronic complication of diabetes mellitus that could develop in any age, any injection site, and be any size. At present time, new method, as ultrasonography of subcutaneous fat, of LIH diagnostics were appeared.

Design
The aim of this study has been to estimate efficiency of insulinotherapy in diabetic patients after LH was diagnosed by ultrasonography of subcutaneous fat with those appearing. This study was done on 50 diabetic patients (31 females and 19 males) who had been under the treatment with insulin a mean 10 years. Ultrasonography of subcutaneous fat was used in assessing LH in typical injection sites. All patients injected insulin in physiological regimen. HbA1c level, fasting and postprandial glucose, episodes of hypoglycaemia, body mass and BMI were evaluated at the moment of LH and after 6 month in all patient. Results were considered to be statistically significant P<0.05.

Results
BMI reduced from 26.34±6.07 kg/m² to 25.25±4.06 kg/m² (P<0.05). Body mass decreased from 72.44±15.73 kg to 70.08±15.02 kg (P<0.05). Also good glycaemic control was demonstrated by measuring glucose and HbA1c level. Thus fasting glucose reduced from 9.03±3.98 mmol/l to 7.11±2.95 mmol/l (P<0.05). Postprandial glucose decreased from 10.27±3.72 mmol/l to 9.34±2.61 mmol/l (P<0.05). HbA1c level reduced from 9.27±2.32% to 7.43±1.52% (P<0.05). Frequency of hypoglycaemia reduced from 1.97±2.23 to 1.10±0.91 in month (P<0.05).

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Conclusions
There were significant improvement of all estimated parameters which characterised the diabetes compensation after changing injected sites because of detected by ultrasonography LH. Since ultrasonography of subcutaneous fat is more sensitive than classic LH diagnostics, it might be used in general clinical practice instead of common detection of LH. Thus, early LH diagnostics can provide to good glycaemic control.
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EP353
Glycoregulation during pregnancy
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Background
Pregnancy presents a state of insulin resistance that can predispose diabetes development in some women, and is associated with increased risk for neonate and for mother. Gestational diabetes is a period of glucose intolerance that manifests at the beginning of the third trimester.

Aim
The aim of this study is to analyse glycoregulation in healthy pregnant women.

Materials and methods
This study included 77 healthy pregnant women in third trimester registered in centre for endocrinology CC Kragujevac that were tested, according to positive 3 h OGTT with 100 g glucose (ADA Criteria), with specifying glycaemia and insulinemia in 0, 60, 120, and 180 min, and HbA1c. According to OGTT results we divided patients in two groups: normal glucose tolerance (NGT) and gestational diabetes mellitus (GDM).

Results
Patients were average 30.8 ± 4.7 (19-41) years old. 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%). The average glycaemia during OGTT in NGT vs GDM in 0 min was 3.92 ± 0.43 vs 4.39 ± 0.46 in 120 min. 6.34 ± 0.99 mmol/l vs 7.14 ± 1.4 mmol/l. From 77 patients, 18 was with GDM (23.3%). As pregnancy progress, disorder of glucose tolerance increased (in second and third trimesters), while 4 weeks after delivery all were with NGT. The average insulinemia during pregnancy was the greater during third trimester in 0 and 60 min in GDM group, in NTG vs GDM in 0 min was 14.81 vs 33.33 ± 16.29, while in 120 min was 198.1 ± 144.25 µIU/ml vs 200.77 ± 120.82 µIU/ml. The average HbA1c during pregnancy was: NTG vs GDM 5.06 ± 0.29% vs 6.1 ± 0.27%.

Conclusion
This research brought for the first time established values of glycaemia during OGTT in healthy women in our population during third trimester, and showed increased prevalence of GDM.
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EP354
Smoking habits and the risk of type 2 diabetes mellitus in women
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Introduction
Type 2 diabetes appears to involve interaction between susceptible genetic backgrounds and environmental factors. It’s important to identify modifiable risk factors for type 2 diabetes, which may help reduce the risk of the disease. The aim of the study was to assess the relationship between smoking and the risk of type 2 diabetes in women.

Methods
In case–control study included 168 cases with a newly confirmed diagnosis of type 2 diabetes during the one whole year and 336 controls which were free of the disease. A specifically designed questionnaire was used to collect information on possible risk factors of type 2 diabetes. Smoking was assessed according to: smoking habits, duration of smoking, number of cigarettes smoked per day, pack years, and smoking cessation. The odds ratios (OR), 95% CIs for type 2 diabetes were calculated by a conditional logistic regression.

Results
The cases had higher BMI and significantly lower education level, compared to the controls. Variables such as family history of diabetes, education, BMI, waist circumference, morning exercise, eating speed, cigarette smoking, occupational and marital statuses were retained in the models as confounders because their inclusion changed the value of the OR by more than 5% in any exposure category. After adjustment for possible confounders increased risk of type 2 diabetes was determined for those, whose smoked ten and more cigarettes per day (OR = 2.83; 95% CI 1.04–7.71 vs non-smokers). It has also been defined an association between the disease and duration of smoking (OR = 4.55; 95% CI 1.11–18.61 for 40 years or more smokers vs non-smokers) and those, whose smoking cessation is 19 years and less had higher risk for diabetes (OR = 6.40; 95% CI 1.50–27.34 vs non-smokers).

Conclusion
Our data support a possible relationship between smoking and the increased risk of type 2 diabetes in women.
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EP355
Optimal glycaemic control and a low rate of micro and macrovascular complications in patients with HNF1A–MODY treated in a dedicated tertiary referral centre
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Objective
HNF1A gene mutations are the most common cause of monogenic diabetes. Patients with HNF1A–MODY display sensitivity to sulphonylurea therapy, however the long term efficacy has yet to be established. There is also limited literature as to the prevalence of complications in this unique cohort. The aim of the study was to determine the natural progression of HNF1A–MODY diabetes in a dedicated MODY clinic.

Design
n=60 HNF1A–MODY mutation carriers and a cohort of n=60 BMI, age, ethnicity, and diabetes duration matched T1DM participated in the study. All subjects were phenotyped. Additional samples were drawn for the cardiovascular biomarkers sCD36/hsCRP. A 12 lead ECG was completed. Peripheral neuropathy and peripheral vascular disease was assessed clinically/ABI. Retinal screening was performed on an annual basis. Detailed clinical follow up of the HNF1A–MODY cohort occurred on a bi-annual basis for 84 months.

Results
Following a genetic diagnosis of MODY the majority of cohort remained insulin independent at 84 months follow up (75%). The HbA1c in the sulphonylurea treated group improved significantly over the study period (55 mmol/mol (45–64) vs 46 mmol/mol (39–58), P=0.009). The group that remained on sulphonylurea therapy alone lost an average of 5.6 kg weight during the study follow up. The rate of retinopathy was significantly lower than that noted in the T1DM group (18.3% vs 50%, P=0.0001). There was also a lower rate of microalbuminuria, neuropathy, and cardiovascular disease in the HNF1A–MODY group than that noted in the T1DM group.

Conclusions
This study demonstrates that the majority of HNF1A–MODY mutation carriers can be maintained successfully on sulphonylurea therapy in the long term. We note a significantly lower rate of micro- and macrovascular complications than that reported in the literature. The use of appropriate therapy at early stages of the disorder and attendance at a dedicated MODY clinic may decrease the rate of complications.

Disclosure
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**EP356**

**Plasma omentin-1 level does not change in the first trimester in women with gestational diabetes mellitus**

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Objective

Gestational diabetes mellitus (GDM) is strongly associated with maternal obesity. Omentin-1 is secreted from the adipose tissue and enhances insulin action. Circulating levels are inversely correlated with body weight, decreased in type 2 diabetes. Pre-existing maternal obesity has been shown to be associated with lower omentin-1 expression in placenta, adipose tissue and maternal plasma. In our previous study, we had shown that plasma omentin-1 level is decreased in women with GDM and increased after delivery. The aim of this study was to assess the maternal plasma omentin-1 level in the first trimester and its predictive value on development of GDM.

Materials and methods

Pregnant women in their first trimester (n = 220) were included into the study. Those that developed GDM (n = 66) was compared with non-diabetic pregnant women (n = 154). WHO criteria was used for the diagnosis of GDM and screening was done at gestational weeks 24–28. Plasma omentin level was measured by ELISA. Fasting blood glucose and insulin were also measured and HOMA-IR was calculated.

Results

Patients with GDM was overweight compared to controls at the beginning of pregnancy (BMI: 28.2±4.4 vs 25.2±3.0). HOMA-IR was higher in GDM group (2.07±1.4 vs 1.40±0.6). Omentin level was not different between groups (2.22±0.8 ng/l vs 2.05±0.9 ng/l). After delivery plasma omentin level increased with a mean level of 166.6±74.1 ng/l. There was no correlation between plasma omentin-1 level and glucose levels during oral glucose tolerance test. Omentin-1 level did not also correlate with BMI, HOMA-IR, and age.

Conclusion

Plasma omentin-1 level during early periods of pregnancy is did not differ between healthy and GDM-developed women. Since decreased levels were observed in GDM patients in previous studies, our findings could indicate that omentin-1 levels decrease as the pregnancy ages or change is only observed when GDM develops.

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**EP357**

**The role of TCF7L2 polymorphism in the development of type 2 diabetes in subjects with metabolic syndrome**

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Introduction

Transcription factor 7 like-2 (TCF7L2) gene variants (rs12255372 and rs7903146) have been consistently shown to raise genetic risk for type 2 diabetes (T2D). The aim of this study was to investigate the possible role of these variants in the development of dysglycemia (T2D or impaired fasting glucose (IFG)) in patients with metabolic syndrome (MS).

Patients and methods

The study population consisted of 228 patients with MS who were divided in two groups. The first group consisted of 148 patients with MS and dysglycemia (39/M(109F), 59.8±14.6 years) and the second group of 80 patients with MS without dysglycemia (16M/64F, 56.1±15.8 years). The diagnosis of MS was based on the criteria proposed by the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) Scientific Statement. The BMI and the waist circumference were recorded and blood samples were obtained after overnight fasting for biochemical tests. The rs12255372 and 7903146 TCF7L2 polymorphisms were genotyped in peripheral blood leukocytes.

Results

Genotype analysis revealed that the frequency of the T allele of the TCF7L2 rs12255372 variant was 38.2% in the study population, while the frequency of the T allele of rs7903146 variant was 35.3%. The T allele of rs12255372 was more frequently present in patients with MS and dysglycaemia (48.3%) compared to patients with MS without dysglycemia (39.4%) (OR: 3.89, 95% CI: 2.47–6.12, P < 0.0001). Also, the T allele of the rs7903146 variant was more frequently found in patients with MS and dysglycemia (44.6%) compared to patients with MS without dysglycemia (18.1%) (OR: 3.64, 95% CI: 2.29–5.78, P < 0.0001).

Conclusion

The presence of variants rs12255372 and rs7903146 of the TCF7L2 gene is associated with dysglycemia (IFG and/or T2D) in patients with MS.

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**EP358**

**Serum irisin level increases throughout the gestational period and it does not play role in development of gestational diabetes mellitus**

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Objective

Irisin is a novel adipomyokine that regulates the differentiation and phenotype of adipose tissue. It induces an increase in total body energy expenditure, improves insulin sensitivity, and glucose tolerance. It showed that the levels of irisin are low in obese, diabetic and impaired glucose tolerance patients. However, the information of the levels of circulating irisin in gestational diabetes mellitus (GDM) is controversial. In this study, we investigated i) the levels of irisin over the first and third trimester of gestation and ii) the change of irisin between first and third trimesters in GDM subjects.

Material and methods

Serum irisin was measured by an ELISA in a longitudinal prospective cohort study in 220 women. There are 154 healthy pregnant and 66 GDM women.

Results

The levels of irisin were low in the first trimester, but higher in the third trimester (0.76±0.54 vs 1.32±0.76, P<0.0001). There was a significant negative correlation between age (P: 0.002, r: −0.207), BMI (P: 0.03, r: −0.188) and weight in the first trimester (P: 0.03, r: −0.185) and HbA1c in the first trimester (P: 0.0001, r: −0.374). There was not any correlation between any parameters and the levels of irisin in the third trimester. The levels of irisin in the first trimester are low but high in the third trimester in the patients with GDM (0.62±0.35 vs 1.26±0.86, P<0.0001). But the levels were not different between women with GDM and healthy controls.

Conclusions

The levels of irisin are low in the first trimester but high in the later stage in third trimester. There is no effect of irisin on the development of GDM. The physiological significance of these findings needs to be assessed in future experiments.

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**EP359**

Gestational diabetes mellitus may associate with atherosclerosis due to high mean platelet volume which is a determined of platelet function

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Aim

Mean platelet volume (MPV), which is a determinant of platelet function, is an independent risk factor for atherosclerosis. The aim of this study is to evaluate MPV values in gestational diabetes mellitus (GDM).

Material and methods

Forty-nine women with gestational diabetes mellitus (mean age 28.2 ± 4.7 years) and 40 healthy pregnant women (mean 26.2 ± 4.6 years age) who came to our Out-Patient Clinic of Endocrinology were included in the study. GDM group and the control group were matched for age. All the study subjects were evaluated by platelet parameters. All complete blood count analysis was performed with an automatic hematologic analyser.

Result

The MPV levels in GDM were significantly higher than those control group (7.9 ± 0.6 and 7.6 ± 0.54 fl, respectively; P = 0.0001). In addition, there was found a positive correlation between MPV and fasting glucose (FG) levels (r = 0.52; P = 0.03). The multiple regression analysis of MPV was performed. High MPV value in GDM was independent from age, BMI, and FG levels (β = 0.338, P = 0.046). No statistically significant differences were found for the other parameters such as haemoglobin, platelet count, lymphocyte count, neutrophil count, white blood cell count, platelet distribution width, and plateletcrit.

Conclusion

Our findings suggest that GDM are susceptible to increased MPV values, which contribute to increased risk of atherosclerosis. Future prospective studies that MPV was compared with other risk factors of atherosclerosis are required to determine their clinically importance in GDM.

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**EP360**

Role of nitrosative and oxidative stress on the development of gestational diabetes mellitus and their effect in GDM placenta

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Background and aims

The relationship between gestational diabetes mellitus (GDM) and oxidative stress is not well known and the effect of both oxidative and nitrosative stress in GDM placenta and the impact that could have on perinatal morbidity and risk of future complications is still pending to be elucidated. The aim of the study was to evaluate the relationships between maternal and placental tissue levels of markers of nitrosative and oxidative stress and antioxidants in women with GDM, which potentially may have considerable clinical implications in the pathogenesis and/or the evolution of GDM.

Material and methods

Pregnant women (n = 78; 53 with GDM, 25 controls), between the 24th and 29th weeks of gestation were enrolled. Both groups were analysed for demographic data, perinatal and obstetrics results and the levels of the markers oxidative stress and antioxidants status were measured (measured in serum or plasma using a commercial kit (Cayman Chemical, Ann Arbor, MI, USA)). Seven placenta GDM and seven normal placentas were studied. Placental tissue levels of markers of oxidative stress and antioxidant were measured by Western Blotting techniques and Biotin-switch technique has been performed to identify S-nitrosylated protein in placental tissue.

Results

In the univariate analysis control versus patient results were: pre-gestational BMI 23.31 ± 4.2 kg/m² vs 27.13 ± 4.6 kg/m² (P = 0.001); weeks at delivery 39.2 ± 3.05 vs 38.9 ± 1.8 (P = 0.09); caesarean delivery 12.5% vs 43% (P = 0.004); macrosomia 4% vs 9.4% (P = 0.6); lipoperoxides (LPO) 2.06 ± 1.00 nmol/ml vs 3.14 ± 1.55 nmol/ml (P = 0.001); catalase 3.23 ± 1.41 nmol/min per ml vs 2.52 ± 1.3 nmol/min per ml (P = 0.03); superoxide dismutase (SOD) 0.11 ± 0.04 U/ml vs 0.01 ± 0.01 U/ml (P = 0.003); glutathione reductase (GSH) 0.004 ± 0.002 nmol/min per ml vs 0.004 ± 0.004 nmol/min per ml (P = 0.9); and glutathione transferase (GST) 0.0025 ± 0.0012 nmol/min per ml vs 0.00017 nmol/min per ml (P = 0.7).

Conclusion

A tendency towards disulfide formation in GDM/placenta was found in patients with diabetes mellitus and there was a positive correlation between Hba1c and disulfide/thiol ratio.

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**EP361**

Dynamic thiol/disulfide homeostasis in patients with newly diagnosed type 2 diabetes mellitus

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Background

Thiol/disulfide homeostasis plays an important role in antioxidative defense mechanism, detoxification, signal transport, management of enzyme activity and transcription factors, and apoptosis. When thiol/disulfide homeostasis breaks down, these important cellular functions get deranged. Pathologies secondary to oxidative stress are seen in organelles in which this homeostasis is deranged. The aim of the study was to investigate dynamic thiol/disulfide homeostasis in newly diagnosed type 2 diabetes mellitus.

Methods and materials

Blood thiol/disulfide homeostasis status, that consists of native thiol–disulfide exchanges, was investigated in 60 patients (22 males and 38 females) diagnosed with type 2 diabetes mellitus and 60 healthy control subjects (25 males and 35 females). Serum native thiol and total thiol concentrations were measured as a function of age. The dynamic thiol/disulfide homeostasis and serum disulfide/thiol ratio were measured in patients with type 2 diabetes mellitus and healthy controls.

Results

In comparison to the control group, patients with diabetes mellitus had lower levels of serum thiol and total thiol (340.7 ± 46.1, 313.7 ± 57.4 μmol/l; P = 0.005 and 366.7 ± 46.7, 343.7 ± 59.0 μmol/l; P = 0.02), while higher average disulfide level (12.9 ± 3.2, 15.0 ± 4.6 μmol/l; P = 0.008). In patients with diabetes mellitus, average disulfide/thiol ratio (% (3.9 ± 1.2 vs 5.0 ± 1.6; P = 0.001) and disulfide/total thiol ratio (% (3.6 ± 1.0 vs 4.5 ± 1.6; P = 0.001) was higher while average thiol/total thiol ratio (%) was lower (92.8 ± 2.1 vs 91.0 ± 3.4; P = 0.001) than the control group. Hba1c level and age correlated positively with serum disulfide/thiol ratio and disulfide/total thiol ratio (r = 0.239, P = 0.009 and r = 0.228, P = 0.012) respectively while thiol/total thiol ratio was correlated negatively (r = −0.228, P = 0.012).

Conclusion

Thiol/disulfide homeostasis in newly diagnosed type 2 diabetes mellitus is deranged.
EP362
The growth patterns in children born to mothers with gestational diabetes mellitus
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Introduction
The aim of the study was to assess if gestational diabetes mellitus (GDM) influence the pregnancy outcomes and the growth patterns in children.

Design
Our prospective study cohort consisted of 261 children born to mothers with GDM and 153 control children born to non-diabetic mothers. In both groups children’s weight, length were assessed. Children were matched for large for gestational age (LGA) (birth weight >90th percentile for gestational age), appropriate for gestational age (AGA) (birth weight between the 10th and 90th percentiles), and small for gestational age (SGA) (birth weight <10th percentile) status. Children anthropometric measurements were made at 12, 18, 24, and 30 months. BMI was calculated. The overweight was diagnosed at BMI between 90 and 96 percentiles, obesity between 97 and 100 percentiles. The WHO child growth standards were implemented. The bioethics committee agreement was obtained.

Results
Among 261 GDM children, 80.5% were AGA, 10% SGA, 9.6% LGA; in control group 19% LGA. Birth weight of the child in GDM pregnancies was 3.30 ± 0.53 kg comparing to the control children 3.42 ± 0.54 kg, P = 0.01. No changes in weight and BMI were found between groups in the 12th month of life. The weight > 90 percentile at this period was observed in 34.6% children, BMI between 90 and 96 percentiles in 17.3% and between 97 and 100 percentiles in 17.3%. At the age of 18 months the weight of children born to GDM mothers was >90 percentile in 54.8% comparing to the control group in 29%, P = 0.04; No changes were found in BMI. At the age of 24 and 30 months we found no differences in BMI in both groups.

Conclusions
We found that children who were LGA at birth were less often born to GDM mothers after implementation of dietary regiment comparing to general population. GDM did not influence the growth pattern in first 36 months of life.

Disclosure
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EP363
Insulin resistance is associated with larger thyroid volume in adults with type 1 diabetes
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Background
Larger thyroid volume and nodular thyroid disease were found to be associated with insulin resistance (IR) in patients with type 2 diabetes (T2DM). Similar analyses is lacking in T1DM.

Aims
To check the association between thyroid volume and IR using estimated glucose disposal rate (eGDR) in patients with T1DM.

Materials and methods
We included 99 consecutive patients with T1DM aged 29 (mean, s.d.) ± 6) with diabetes duration 13 (6) years. Exclusion criteria were: history of thyroid disease, current treatment of t-choy hormone or anti-thyroid drugs. Anti-thyroid peroxidase (ATPO), anti-thyroglobulin (ATg) antibodies, and anti-TSH receptor antibodies (TRab) were determined. Assays for TSH and free thyroid hormones (triiodothyronine, T3, and thyroxine (T4)), were also performed. Thyroid was measured using ultrasonography. IR was assessed using eGDR, calculated according to the formula (24.4 ± 12.97/ WHR − 3.39 × HT − 0.60 × HB/AC), where WHR - waist-to-hip ratio and HT – history of hypertension (yes = 1 and no = 0).

Results
The prevalence of thyroid autoimmunity (positivity for ATPO, ATg, or TRab) in the study group was 31%. Subclinical hypothyroidism was diagnosed in 7%, and overt hypothyroidism in 2% of patients. Mean (s.d.) thyroid volume was 15.6 (6.2) ml in patients with eGDR ≤ 7.5 (patients with IR) and 11.7 (4.7) ml in patients with eGDR above 7.5 (P = 0.002). Thyroid volume correlated inversely with eGDR (r = −0.35, P < 0.001). In multivariate linear regression model association between thyroid volume and eGDR was independent from sex, duration of diabetes, BMI, TSH, and presence of thyroid autoimmunity (β = −0.22, P = 0.025).

Conclusion
Lower insulin sensitivity is associated with larger thyroid volume in patients with T1DM independently from BMI and signs of autoimmune thyroid disease.

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EP364
Rate of impaired glucose regulation in outpatient care
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The objective was to assess rate of impaired glucose regulation and progression to diabetes in adults using routinely collected health-care data.

Material and methods
We conducted an audit on results of 75-g standardized oral glucose tolerance tests (OGTT) performed at Vilnius Antakalnio Outpatient Clinic from 3rd Jan 2011 to 15th Dec 2014 and analysed data of adult patients. We excluded from analysis results of 358 patients who didn’t perform 2-h plasma glucose concentration (2 h PG) test. 5575 patients’ data were included into analysis. We applied 2006 World Health Organization criteria for diabetes, impaired glucose tolerance (IGT) and impaired fasting glucose (IFG).

Results
Mean patients’ age was 53.64 ± 15.59 years. 36.4% of the patients were men and 63.6% were women. Mean fasting plasma glucose (FPG) concentration was 5.87 ± 0.65 mmol/l, mean 2 h PG was 6.20 ± 2.25 mmol/l. FPG in women was lower than in men (5.79 ± 0.67 mmol/l vs 6.03 ± 0.60 mmol/l, P < 0.001), but 2 h PG was higher in women than in men (6.25 ±2.14 mmol/l vs 6.09 ± 2.44 mmol/l, P < 0.011). Mean 2 h PG increased with age. OGTT detected diabetes in 286 (5.1%) patients. 778 (14.0%) patients met criteria for IGT and 1518 (27.2%) for IFG. Normal glucose tolerance was found in 2993 patients. The rate of impaired glucose regulation increased with age achieving peak in groups of 50–59 and 60–69 years old patients (27.3 and 23.4% respectively). 787 patients came back for repeated OGTT. Repeated OGTT revealed 48 new cases of diabetes. Before developing diabetes 58.3% patients had IGT, 22.9% had IFG, and 18.8% had normal glucose tolerance. Mean time from the first OGTT to diabetes development was 18.15 ± 9.36 months. Female gender (OR = 2.42, P = 0.028) and IGT (OR = 6.08, P < 0.001) predicted diabetes.

Conclusion
This analysis revealed that the rate of undiagnosed diabetes is 5.1%; nearly half of outpatients with risk factors for diabetes have impaired glucose regulation. Women with IGT have higher risk for diabetes development.

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EP365
The prevalence of diabetes and associated risk factors among adult population in a Turkish population (Trabzon city)
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Objective
The objectives of this study were to determine the prevalence of diagnosed and undiagnosed diabetes mellitus (DM), prediabetes and to evaluate the associated risk factors in the sample of adult Turkish population.

Methods
A total of 4000 eligible study subjects aged 20 years or older, chosen by multistage sampling on a field were selected. Of those 3721 subjects (2139 women and 1582 men) participated in the study. The study was performed between January 2010 and September 2012 in central Trabzon and its ten town.

Results
The prevalences of prediabetes and DM were found to be as 6.4 and 10.4% (newdiagnosed 3.6%) respectively. There was no a significant difference between men and women for the prevalence of diabetes. Diabetic prevalence was found to
increase significantly by aging in both genders ($P<0.0005$). The prevalence reached its peak level in age group of ≥70 years (29.2%). In multivariate logistic regression analysis, advanced age (OR: 21.6 in the 60–69 age group and OR: 26.7 in the group 70 years and over), marriage (OR: 2.05), housewives (OR: 1.34), high monthly income (OR: 2.92 in the group of income ≥2250 TL), positive family history of diabetes (OR: 2.84), overweight (OR: 1.61), obesity (OR: 2.25), hypertension (OR: 1.42), and dyslipidaemia (OR: 1.38) were independent risk factors for the development of diabetes.

Conclusion

DM is an important health problem in the adult population of Trabzon city. It seems that the prevalence of diabetes is increasing in our region as well as our country and the world. New diagnosed diabetic patients who are unaware of their status are at high risk. To control DM and associated risk factors, effective public health education and taking urgent steps including serious education and teaching, providing a well-balanced diet and increasing physical activity are needed.

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**EP366**

Diabetes mellitus in patients with rheumatoid arthritis

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Introduction

In rheumatoid arthritis (RA) glucose metabolism may be affected either by the autoimmune inflammatory disease itself, or by the treatment used to manage the disease. Metabolic syndrome seems to be prevalent in RA patients.

Aim

The aim was to study the prevalence of diabetes mellitus type 2 and metabolic factors related to the development of atherosclerosis within a cohort of RA patients cared for within a single Rheumatology Department.

Methods

Within a cohort of 204 RA patients, aged 29–88 (mean ± S.E.M.) 62.87±0.86 years, the incidence of diabetes mellitus and metabolic factors related to the development of atherosclerosis was studied. In the cohort of RA patients ESR was 37.12±1.57 mm/h, CRP 1.56±0.15 mg/dl, and the disease activity index DAS28 was 3.80±0.13, 49% being positive for rheumatoid factor and 25% having positive anti-CCP antibodies.

Results

Within the cohort of 204 RA patients 45 (22.06%) were found to suffer from diabetes mellitus type 2, five being on therapy with a combination of insulin and oral antidiabetic agents, ten on oral antidiabetic agents, and the rest on diet only. Within the cohort of RA patients morning glucose concentration was 110±3.09 m/dl and NGT, 1.57 m/dl, cholesterol concentration 200.3±2.98 mg/dl, HDL cholesterol 55.64±1.18 mg/dl, LDL cholesterol 123.19±2.41 mg/dl, and triglyceride 123.4±3.73 mg/dl. Within the cohort of RA patients 33 had hyperlipidaemia requiring therapy with lipid lowering agents, mainly statins and in two cases a combination of statin and fenofibrate.

Conclusions

Diabetes mellitus type 2 seems to be prevalent amongst patients with RA, hyperlipidaemia being also prevalent. The disease itself, which is related to an autoimmune inflammatory process and the medications required for its management may affect blood glucose metabolism adversely.

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**EP367**

Correlation between fasting plasma glucose levels and HbA1c for diagnosis of prediabetes and diabetes: the 2011 Korea National Health and Nutrition Examination Survey

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Aim

HbA1c is recommended as a diagnostic criterion for diabetes in clinical practice guidelines for type 2 diabetes in 2011 (10). Although there have been several reports that compared HbA1c-based diagnosis for diabetes with glucose-based diagnosis in Koreans, it is thought that larger epidemiological studies are required to confirm the association of HbA1c and FPG for diagnosis of diabetes for the Korean population. We conducted this study to examine the relationship between FPG and HbA1c levels measured for diagnosis of diabetes and assess the differences in FPG and HbA1c values according to the HbA1c-based and FPG-based diagnosis of diabetes recommended from the ADA in the recent Korea National Health and Nutrition Examination Survey (KNHANES).

Methods

KNHANES, conducted periodically by the Korea Centers for Disease Control and Prevention and initiated in 1998, designed to provide comprehensive information of Korean on health status, health behavior, and nutritional states. Data from second (2011) years KNHANES V (fifth) which samplings include HbA1c over 10 years old men and women and fasting blood glucose were used in this cross-sectional analysis. From an initial total of 8518 men and women, 6066 persons (2677 men and 3389 women), with HbA1c and fasting glucose data and without diabetic medications, were evaluated. From 6066 persons, 1585 were excluded for several reasons. Baseline characteristics are presented as means for continuous variables, and proportions for categorical variables. The association of fasting blood glucose and HbA1c was examined using linear regression models.

Results

We found the results of linear regression analysis in the study population and in the subjects with diabetes by FBS criteria only. FPG 100 mg/dl, predicted HbA1c 5.75% in the study population and 5.76 in the subjects with diabetes by FBS criteria only respectively. FPG 126 mg/dl also predicted HbA1c 6.4% and 6.44%. However, in the subjects with diabetes by HbA1c criteria only, FPG 100 mg/dl, predicted HbA1c 6.49%, FPG 126 and 130 mg/dl, and predicted HbA1c 7.14 and 7.24% respectively.

Conclusions

This study is the first epidemiological report showing that an association between HbA1c and FPG levels for the diagnosis of prediabetes and diabetes is consistent with ADA recommendations in over 19 years old Korean population without diabetic medications. This conclusion requires further study to compare the characteristics of individuals with newly diagnosed diabetes by each only HbA1c- and only FPG-based diagnostic criteria and large-scale longitudinal study to assess the relation of HbA1c to incident diabetic retinopathy.

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**EP368**

Blood lead is associated with impaired fasting glucose in middle-aged population: the 2008–2011 Korean National Health and Nutrition Examination Survey

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Objective

Environmental exposure to heavy metals has affected human health. Several studies have suggested that lead increase oxidative stress and induce mitochondrial dysfunction. The objective was to determine whether there was an association between blood lead level and impaired fasting glucose (IFG) in middle-aged population.

Research design and methods

This study was based on the data from the Korean National Health and Nutrition Examination Survey (KNHANES), conducted by the Korean Ministry of Health and Welfare in 2008–2011. Of 37 753 participants, data for 2366 adults ≥40 years of age without diabetes were included in the analysis. Subjects were subdivided according to quartile of blood lead level. Multivariate logistic regression analyses were used to identify whether there was an independent association between blood lead level and IFG by adjusting for confounding factors.

Results

Blood concentration of lead was significantly higher in IFG group, compared with normoglycemia glucose tolerance (NGT) group (IFG, 2.72±0.565 μg/dl and NGT, 2.52±0.384, P = 0.002). The prevalence of IFG increased significantly by increasing quartile of blood lead level (Q1, 20.6%; Q2, 21.6%; Q3, 26.7%; and Q4, 31.1%; P = 0.001). After fully adjusting for confounding factors, including lifestyle behaviors, sociodemographic factors, family history of diabetes, and known diabetes risk factors, the fourth quartile of blood lead level (> 3.091 μg/dl) was significantly associated with IFG (odds ratio 1.491 (95% CI 1.004–2.214)).

Conclusions

Blood lead level was independently associated with IFG in middle-aged population. We propose that the lead may contribute to increasing glucose level and risk of prediabetes.

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**EP369**

The state of superoxidedismutase activity as marker of oxidative stress in patients with impaired glycaemic states

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One of the key enzymes of antioxidant system is superoxide dismutase (SOD) that catalyses dismutation of superoxide anionic radical (O_2^-) into molecular oxygen (O_2) and hydrogen peroxide (H_2O_2). It was revealed that activity of SOD is decreased in patients with decompensecated type 2 diabetes (T2D) but there is insufficient data about enzyme activity in compensated states and prediabetes.

**Purpose**

To analyse the state of SOD activity in patients with compensated T2D and prediabetes.

**Materials and methods**

195 patients were divided into five groups: group 1 – 23 patients with impaired fasting glucose (IFG), group 2 – 23 patients with impaired glucose tolerance (IGT), group 3 – 41 patients with T2D, group 4 – 48 patients with T2D and concomitant coronary heart disease (CHD), and group 5 – 41 almost healthy person (control). All patients were before 60 years old and patients with T2D had compensated glycaemic state. Activity of SOD was measured by reduction of nitrobtetrazolium by superoxide radical.

**Results**

The lowest activity was registered in group 4 (71.71 (48.14; 80.37) CU/ml) and in group 3 (76.49 (35.43; 85.22) CU/ml) compared to control group (104.96 (66.86; 142.82) CU/ml) (P<0.001). Activity of SOD was significantly lower in patients with IGT (92.95 (60.21; 144.02)) compared to control group (104.96 (66.86; 142.82) CU/ml) (P<0.005 and P<0.001 respectively). On ROC curves, the AUC for AARR was 0.905 (95% CI 0.821–0.988) and for ARR 0.947 (95% CI 0.903–0.991) were not significantly different.

**Conclusions**

The automated aldosterone and renin chemiluminescent assay is a reliable alternative to the well-established radioimmunometric method, especially for the detection of APA.

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**EP370**

Comparison between aldosterone and renin measurement by chemiluminescent immunoassay and RIA for the diagnosis of primary aldosteronism

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**Objective**

Primary aldosteronism (PA) is the most frequent cause of secondary hypertension. According to the Endocrine Society Guidelines, up to 50% of hypertensive patients should be screened for PA, using the aldosterone to renin (plasma renin activity (PRA)) ratio (AARR and ARR respectively). The automated Diasorin LIASON chemiluminescent immunoassay for renin and aldosterone measurement became available and in many laboratories is currently used instead of the classical radioimmununometric PRA and aldosterone assay. Aim of the study was to prospectively compare the diagnostic accuracy of AARR and ARR as screening test for PA and the two aldosterone assays also during confirmatory test in patients with a positive screening test.

**Design and methods**

100 patients were screened for PA and 44 patients underwent confirmatory test (i.e. saline load or captopril challenge test). We considered as cut off for the AARR 2.7 (ng/dl/mU/l) and for the ARR 30 (ng/dl/ng/ml/h). All patients positive to one of the two screening test underwent confirmatory test; patients with positive confirmatory test underwent subtype diagnosis by CT scanning and adrenal vein sampling.

**Results**

73 patients were diagnosed as essential hypertensives, 22 had bilateral adrenal hyperplasia, and five had an aldosterone producing adenoma (APA). The AARR displayed a sensitivity of 78% and a specificity of 100%, whereas the ARR had a sensitivity of 96% and a specificity of 99%. Of the 6/27 PA patients missed by AARR, none resulted to be affected by APA. All PA patients were correctly diagnosed by chemiluminescence at confirmatory test. In the overall sample of 181 measurements available both the correlation for the PRA with renin and for aldosterone in chemiluminescence and RIA were highly significant (r=0.66, P<0.0001 and r=0.80, P<0.0001 respectively). On ROC curves, the AUC for AARR was 0.905 (95% CI 0.821–0.988) and for ARR 0.947 (95% CI 0.903–0.991) were not significantly different.

**Conclusions**

Pre-gestational diabetic women are highly self-motivated as shown by this qualitative research. 'SDSCA' questionnaire surprisingly did not detect significant changes, yet considerable changes in self-care were reported at interview. In conclusion, pre-gestational diabetic women are highly self-motivated as shown by this qualitative research. 'SDSCA' was not sensitive in this setting.

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**EP371**

Listening to the patient’s story: a qualitative approach to pre-gestational diabetic pregnancy

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**Aim**

Pre-gestational diabetes frequently rise to the challenge of pregnancy with remarkable improvements in diabetic control. Optimising pregnancy outcomes necessitates rigorous diabetes self-care, which is critically dependent on women’s capacity and the support they receive. The aim of this study was to identify self-reported drivers and inhibitors of self-care in pre-gestational diabetic pregnancies.

The study was carried out at a tertiary referral maternity unit. Convenience sampling was used. Ten women were recruited: age range 20–40 years, median age 33 years; nine type 1 diabetics; one type 2 diabetic; duration of diabetes ranged from 1 to 33 years, median was 16.5 years; 6 were unplanned pregnancies; six primigravida; two received diagnosis of foetal complications. Baseline Hba1c ranged from 42 to 85 mmol/l, median was 73 mmol/l. Follow-up measures ranged from 35 to 53 mmol/l, median was 48 mmol/l. Qualitative methods were employed to extract novel insights. We interviewed ten pregnant diabetics using six open-ended questions. Audio recordings were transcribed and 'computer assisted qualitative data analysis software' (CAQDAS) assisted coding and analysis of transcripts. Content analysis of transcripts revealed numerous themes. In addition, changes in self-care during pregnancy were measured using a validated questionnaire, 'Summary of Diabetes Self-Care Activities' ('SDSCA'). Nine women reported being highly motivated, driven predominantly by concern for baby’s wellbeing. Numerous challenges were identified: difficulty maintaining a strict diet, hypoglycaemia, turbulent blood glucose and emotional challenges. Women perceived the glycaemic targets as demanding. In contrast numerous supports were perceived to facilitate self-care, particularly the diabetic care team. Other supports were family and the working environment. Regular daily routine was viewed as crucial. The 'SDSCA' questionnaire surprisingly did not detect significant changes, yet considerable changes in self-care were reported at interview. In conclusion, pre-gestational diabetic women are highly self-motivated as shown by this qualitative research. 'SDSCA' was not sensitive in this setting.

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**EP372**

Biorythms of constrinuous hormones in pregnant with type 1 diabetes receiving insulin with pump therapy and multiple injections

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**Aim**

To examine circadian biorythms of constrinuous hormones (BCh) contribution in the morning postprandial glycaemia depending on the type insulin therapy.

**Materials and methods**

The study involved of 91 pregnant with T1D in 31–34 weeks on a background the maximum insulin resistance. Evaluation of circadian BCh (cortisol, progesterone, and placental lactogen) held on the results of the ELISA (DRG, Germany) serum samples, pick ups in 0300, 0700, 1200, 1700, and 2200 h.
EP373
Higher glucose levels and prevalence of prediabetes in patients with autoimmune thyroiditis
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Introduction
Thyroid autoimmunity and diabetes mellitus type 2 (DM2) are the commonest endocrine disorders in the general population. The aim of the study was to investigate whether there is an association between thyroid autoimmunity and β-cell secretion in patients with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT).

Methods/design
501 patients (381 females) 46.5±14.2 years with IFG and/or IGT and autoimmune thyroiditis (AIT, TgAb, and/or TPOAb positive) were included in the study. Characteristics recorded were age, gender, waist circumference (cm), and BMI (kg/m²). Fasting glucose (mg/dl) and insulin levels (µM/ml), glucose 120 min post-oral glucose tolerance test (OGTT), HbA1c (%), HOMA and QUICKI insulin-resistance (IR) indices, and IR status as HOMA > 2.16 and QUICKI < 0.34 were also assessed. In 291 patients who had an oral glucose tolerance test (OGTT) with glucose and insulin measurement in five different time points, first, second phase insulin sensitivity index (ISI) and ISI were also assessed. Patients with hypothyroidism and DM2 were excluded from the study.

Results
Patients (n = 266) who had AIT compared to non-AIT patients (n = 235) were older (48.6±13.5 vs 44.1±14.66 (P = 0.001)), had larger waist (95.4±15.6 vs 91.4±15.5 (P = 0.007)), higher glucose levels (99.9±12 vs 95.5±12.5 (P < 0.001)), and lower prediabetes rates (64.2%) (χ² = 27.2, P <0.001) but similar rates of IR (51.8%). Prediabetic (P = 64) patients with AIT had first phase ISI: 1293.8±774.6, second phase ISI: 432.3±231.8, and ISI: 0.06±0.05 comparable albeit higher to non-AIT (first phase ISI: 934.3±670.5 second phase ISI: 324.8±207.9, and ISI: 0.07±0.05) but similar ISI (P = 0.06, P = 0.06, and P =0.6 respectively).

Conclusion
Patients with AIT and impaired β-cell secretion had higher HbA1c levels with similar rate of insulin resistance and higher prevalence of prediabetes compared to non-AIT. Thyroid autoimmunity could be eventually a possible factor modifying β-cell secretion. Nevertheless further studies are needed to confirm these findings.

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EP374
Effectiveness of Aβ classification of diabetes prone to ketosis in real clinical practice
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Introduction
Prevalence of so-called diabetes prone to ketosis (DPK), has been increasing. The necessity of lifelong insulinotherapy is determined by Aβ classification of DPK.

Design
Seven patients with atypical course of T2DM were studied. All patients had gradual development of hyperglycemia, obesity 1–2 stages, and acetonuria. Noone had acute weight loss. Stage 3 had positive GAD-AB, stage 4 – negative. Initially all patients were treated by insulin during 2–3 weeks. Thereafter, C-peptide was determined and type of diabetes, prone to ketosis, was established. If C-peptide was more than 1.2 ng/ml, oral hypoglycemic drugs were prescribed. Patients were followed up during 1 year with studying BMI, C-peptide, HbA1c, and acetonuria.

Results
Three patients had diagnosis of A+β-DPK and took oral medicine. However, during 1-year follow up, all these patients had HbA1c greater 7.5%, uncontrolled weight loss and periodical acetonuria. After 6-month of follow up C-peptide was <1.2 ng/ml at all patients, which was an indication to lifelong insulinotherapy. Four patients were diagnosed with DPK A – β- and took oral medicine. During 1-year follow up, 2 patients had HbA1c <7.5% and no cases of acetonuria. With stable weight, the level of C-peptide was still >1.2 ng/ml at the end of follow up. Thus, the prescribed treatment with oral hypoglycemic agents were continued. Two patients had HbA1c >7.5%, frequent cases of acetonuria and significant weight loss. C-peptide were declining progressively during 1-year follow up. That’s why the diagnosis was changed to DPK A – β-+, and lifelong insulinotherapy was prescribed.

Conclusions
Current Aβ classification of DPK is thought to allow to determine necessity of year-long insulinotherapy, which were not proved in our pilot study. The more clinical experience is needed to make strict follow up and treatment recommendations for patients with atypical diabetes.

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EP375
Evaluation of quality indicators in hospital discharge reports in diabetic patients from an Internal Medicine Service: are we doing a good clinical practice?
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Spanish Scientific Societies involved in diabetic patient care produced a consensus document with recommendations and quality indicators for hospital discharge reports (HDR).

Objective
To analyse adequacy of HDR in diabetic patients from an Internal Medicine Service according to these recommendations (Med Clin (Bar) 2012 138 666.e1–666.e10).

Methods
Study based on a programme continuity of care among Primary Care and Internal Medicine Service. We analyse 150 consecutive HDR in diabetic patients from an internal medicine service of a tertiary hospital. HDR were identified by hospital database and five cases were excluded by death. Clinical information was revised according to nine items recommended in document consensus.

Results
Average age 73.5 years, men 47% and women 53%. T2D 96%, 2% T1D, and steroid diabetes 2%. Diabetes de novo was present in five cases (3.4%). Time evolution diabetes was recorded in 27% of HDR and HbA1c only in 17.8%. Renal function (MDRD-4); Normal FGR 26.8%, 18.5% CKD stage 2, 3 33.5%, stage 4 15.7%, and stage 5 5.5%; however, FGR only was recorded in 9% HDR. Antidiabetic treatment prediagnosis was not collected in 36.3%. Where it was present were: monotherapy oral antidiabetic agents (OAA) 26.7%, 8.9% combination OAA, OAA more insulin 9.5%, alone insulin 18.6%. At discharge changes were made in the treatment at 35% but only 23.2% consisted justification at HDR. Changes were: first insulinisation 19.8%, OAA substitution 7.5%, and replacing insulin type 7.7%. The 45% of HDR collected recommendations on diet and exercise, glycaemic control targets in 7.5%, other control cardiovascular risk factors 9.5%, periodicity 13% glycaemic control and medical supervision (within review and assistance level) 11%.

Conclusions
Quality of HDR diabetic patients is low compared with the established recommendations. An improvement program should be introduced to optimise and tailor treatment in diabetic patients at hospital discharge.

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EP376
Gonadal hormone regulates the expression MATE1 and OCT2 in type 2 diabetes mice
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Background and aims
Multi-drug and toxin extrusion 1 (MATE1) and organic cation transporters 2 (OCT2) are important proteins of metformin transport and excretion in liver and kidney. Our previous study showed that there were gender difference of metformin’s hypoglycemic effect and it was independently linked with the oestrogen and testosterone levels in type 2 diabetes patients. This study was designed to observe the impact of oestrogen and androgen on the renal expression of MATE1 and OCT2 in female and male db/db diabetic mice.

Materials and methods
Eight week-old db/db and their normal control mice were divided into hormone intervention group (n = 20) which were injected testosterone 10 mg/kg per day (n = 10) or oestradiol 1 mg/kg per day (n = 10) for 7 consecutive days, and control group (n = 10) received the same volume of olive oil for 7 days. Both the intervention group included male subgroup (n = 10) and female subgroup (n = 10), respectively, and also had normal control group (n = 5). The blood were collected to detect plasma testosterone or oestradiol levels at day 7, the RNA and protein were extracted from kidney tissue to detect the expression of MATE1 protein and OCT2 mRNA and protein with western blot and real-time PCR.

Results
i) After treatment with exogenous hormones, plasma levels of oestrogen (6.2 ± 1.3 vs 5.0 ± 0.94) and androgen (92 ± 23 vs 64 ± 9) increased markedly in both male and female mice (P < 0.01). ii) Renal OCT2 mRNA levels in testosterone-treated male (TM) and female (TF) mice were significantly higher than control female mice (CF, 2.6 ± 3.78, P < 0.05). On the contrary, treatment with oestradiol in both of males (EM) and females (EF) had no significant impact on OCT2 mRNA expression (both P > 0.05). Simultaneously, the MATE1 mRNA levels in testosterone-treated male group increased significantly compared to control male mice (CM, P < 0.05) and oestradiol-treated male mice (P < 0.05). No obvious changes of MATE1 mRNA levels were found in both EM and EF (P > 0.05). iii) The expression of OCT2 protein in TM was significantly higher than that of CF (P < 0.05). However, the expression of both the MATE1 and OCT2 protein levels in TM group were higher markedly compared to CM (P < 0.05). In oestradiol-treated males, the MATE1 expression elevated significantly (P < 0.05), but the OCT2 expression had no apparent change (P > 0.05).

Conclusions
Oestrogen and androgen up-regulate MATE1 expression of kidney in male diabetic mice, but have little effect on that of female mice; androgen increases OCT2 expression both in male and female mice, but oestrogen has little effect on their OCT2 expression.

Disclosure
This study was supported by grant from National Natural Science Foundation of China (81707050 for F Liu).

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EP377
The clinical effectiveness of screening for gestational diabetes mellitus in primary vs secondary care: results of a randomised controlled trial
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Aims
The aim of this paper is to report on the outcomes of a clinical trial investigating the clinical effectiveness of universal screening for gestational diabetes mellitus (GDM) in primary care vs secondary care. Design and methods
A parallel group randomised controlled trial of universal screening for GDM in primary vs secondary care. The primary outcome – uptake of screening in primary vs secondary care is reported elsewhere. In this article we report on the secondary outcomes of the trial: i) GDM prevalence, ii) timing of screening, iii) time to access antenatal diabetes care, and iv) maternal and neonatal outcomes.

Results
The prevalence of GDM was similar in primary care and secondary care screening groups, and groups were comparable in terms of the timeliness of screening, with both groups receiving screening at a mean of ~26 weeks. However there was a considerable delay (in both groups) in the time to access hospital treatment for women with GDM. For patients screened in the hospital the delay is 19 days, for those screened at the GP the delay is 24 days. Further research is needed to understand the reasons for this delay. In addition the GP group had a higher proportion of large for gestational age infants than the hospital group. It is possible that the delay in access to care is implicated in the increased infant size in this group; further research on a larger sample will be needed to answer this question. There were no differences between groups in maternal outcomes.

Conclusions
The evidence presented in this paper, shows that the hospital is still the best option for GDM screening, in terms of access to screening and in terms of time to access hospital care for those with GDM. Implications for long term GDM care are discussed.

Disclosure
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EP378
Risks of having gestational diabetes in the future for mothers and their offspring
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Introduction
Gestational diabetes (GDM) has an important short and long-term health consequences for both the mother and her offspring. The aim of this study was to evaluate current metabolic status of women with GDM history and their offspring approximately at 10th year after delivery.

Methods
24 mothers who had GDM 10 years before (mean age 41.08 ± 4.13 years and BMI 30.3 ± 5.9) and their children (11 females, 13 males; mean age of 11.0 ± 1.9 years) were enrolled into the study. To evaluate current metabolic status of mothers, 75 g OGTT was performed and according to ADA criteria they were classified into two groups as normal glucose tolerance (group 1: NGT) and glucose intolerance (group 2: IGT and/or DM). Outcomes of foetal determinants were recorded and current clinical status and laboratory features of offspring were checked and evaluated if there would be any associations with mothers’ metabolic status.

Results
41.6% of mothers had any degree of glucose intolerance at 10th year after delivery. As we concluded foetal determinants in groups, measurements of birth weight (g), length (cm) were found as 3625.6 ± 680 vs 3197.6 ± 608; 147.6 ± 11.5 vs 146.7 ± 13.0 respectively. As we considered daily status of children, their BMI and waist circumferences were observed as 18.4 ± 3.1 kg/m² vs 20.6 ± 5.7 kg/m² and 67.7 ± 12.2 cm vs 71.9 ± 10.1 cm respectively (P > 0.05). Although the difference was not significant, waist circumference and central obesity of offspring in group 2 was found higher. Also results of fasting glucose and insulin levels of children in group 2 were higher than the others; but difference was not statistically significant. Five of them had lipid profile changes.

Conclusion
Frequency of glucose intolerance may be increased in the follow-up years; offspring of mothers having prediabetes may have great risk for obesity and insulin resistance in the future; especially at pubertal period. Those adolescents should be identified and efforts should be done to prevent development of metabolic syndrome and lifestyle should be planned to preserve beta cell function of the pancreas before puberty.

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EP379

Maintenance of risk reduction during 3-year follow up in prevention of type 2 diabetes by lifestyle intervention in primary health care setting: Diabetes in Europe Prevention using Lifestyle, physical Activity and Nutritional intervention (DE-PLAN) project

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Introduction

Extended up to 20 years follow-up of several randomised control trials showed 34–43% diabetes risk reduction. Real life implementation studies performed worldwide in different settings and populations proved that also non-intensive, low budget lifestyle interventions can be effective. However little is known about long-term results of the translational studies.

Objective

To study the risk factors changes of the DEPLAN non-intensive lifestyle intervention in primary health care setting during 3-year follow up.

Research design and methods

Study participants (n = 114) with baseline diabetes type 2 risk FINDRISC > 14, no diabetes, received ten group lifestyle counselling sessions, six motivation phones, and two letters and physical activity. Measurements performed at 12 months after the initiation of the intervention were repeated after 36 months.

Results

Statistical significant risk reduction at 1 year was maintained at 3 years in weight (62.9 vs 81.6 kg), BMI (31.2 vs 30.1 kg/m²), serum total cholesterol (5.5 vs 5.4 mmol/l), TG (1.85 vs 1.6 mmol/l (P<0.09)), and FINDRISC (18.4 vs 16.2 (P < 0.05)). After 3 years 6% of participants converted to diabetes, while 56% of baseline IFG and IGT reverted to NGT. Physical activity increase, increased consumption of vegetable and fruit and decreased of saturated fat and change of saturated fat to unsaturated observed at one year were also maintained during follow up (P<0.05).

Conclusions

Diabetes type 2 prevention through non intensive, real life lifestyle intervention with modest weight reduction is feasible in a primary health care setting and can be maintained during long time observation.

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EP380

Discrepancies between the HbA1c criteria and glucose-based criteria for diagnosis of diabetes and pre-diabetes

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The number of the people with type 2 diabetes is increasing globally, therefore there is an increasing need to identify diabetes earlier and more efficiently. Nearly 80% of people with diabetes live in low and middle income countries (LMICs). Traditionally, we have relied on glucose-based criteria (fasting, postprandial, and random) to make the diagnosis of diabetes; however, HbA1c has recently been endorsed as a diagnostic test, as superior alternative to glucose-based criteria. It is still controversial about implementation of HbA1c criteria in LMICs especially due to several cons one of them being high cost. Previous studies have suggested that some degree of discrepancies exist between the HbA1c and glucose based criteria and may vary by race, ethnicity, sex, and age in various populations. Hence, we aimed to access the discrepancies between the new HbA1c-based criteria over glucose-based criteria for diagnosis of diabetes and pre-diabetes among clinically diagnosed Nepalese population. A total of 1277 clinically suspected type 2 diabetes and pre-diabetes who attended Tribhuvan University Teaching Hospital (TUTH), Kathmandu, Nepal between January 2012 and April 2014 were recruited in the study. Initial screening was carried out using the FINDRISC questionnaire. The American Diabetes Association (ADA)-glucose based and ADA-HbA1c criterions were used to diagnose diabetes and pre-diabetes. The discrepancies between two criteria to diagnose pre-diabetes and diabetes were evaluated. Significant discordance exists between the HbA1c- and glucose-based criteria for diagnosis of diabetes in Nepalese population. Furthermore, the substantial numbers of subjects with pre-diabetes were missed by HbA1c criterion.

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EP381

The correlation of serum ferritin and diabetes, glucose control or insulin resistance, related or not?

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Background

We have previously investigated the association between serum ferritin levels and risks of metabolic syndrome (MetS) using the same database from 2009 wave of the China Health and Nutrition Survey (2009 CHNS). We confirmed that MetS components are associated with increased serum ferritin levels in both men and women groups, included abdominal obesity, hyperglycemia, low HDL cholesterol, high blood pressure, and abnormal glucose level. Although, the prevalence of anaemia was not associated with having diabetes, the anaemic participants have abnormal iron metabolism. This will influence the serum ferritin levels. In this study, we aimed to further investigate the association between serum ferritin concentrations with diabetes, glucose control and IR adjusted for other confounders in non-anaemic Chinese population, especially adjusted other MetS components in multivariable logistic regression analyses.

Methods

Fasting blood samples and anthropometric data collected on 7362 adults aged 18 and older in 2009 wave of the China Health and Nutrition Survey (2009 CHNS). Data were collected by trained physicians. The fasting serum glucose and blood glucose level was measured at local hospitals. Other biochemical markers were analyzed by an automatic clinical chemistry analyser at the Department of Laboratory Medicine of CJFH.

Results

For both men and women, higher concentrations of serum ferritin were associated with higher values for markers of insulin resistance. But after adjusted for age, and some of MetS components, the difference became weak.

Conclusion

We observed a weak association between serum ferritin levels and the prevalence of diabetes and IR in non-anaemic population. Additional studies are needed to elucidate the mechanisms of serum ferritin and risks of diabetes. This may help to reduce diabetes or pre-diabetes.

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EP382

Impact of ACE gene polymorphism on preeclampsia development and insulin resistance aggravation in pregnant women with type 1 diabetes mellitus

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Type 1 diabetes mellitus (T1DM) and preeclampsia (PE) in pregnant women share common pathophysiological pattern (hypovolemia, increased vascular resistance, and kidney damage) and both are genetically determined. Genetic impact on PE development and aggravation of insulin resistance in T1DM pregnant women has been underinvestigated. Thus, the aim of this case-control study was to evaluate the influence of ACE gene ID polymorphism on risk of PE and insulin resistance development.

Materials and methods

Inclusion criteria were as following: for group I – T1DM with superimposed PE (30 patients) and for group II – DM without PE (30 patients). Standard examination was undertaken during pregnancy and postpartum, as well as detection of ACE gene polymorphism with allele-specific PCR. The obtained results were analysed using STATISTICA 10.0 Software.

Results

Patients of group II had significantly higher prevalence (χ² = 10.35; P < 0.01) of II genotype compared to group I (56.7 and 16.7% respectively) supporting the
**EP383**

Mechanisms of development of carbohydrate metabolism disturbances in acromegalic patients depending on treatment

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**Background**

In acromegaly, carbohydrate metabolism disorders (CMD) are frequently observed. The effect of therapy of acromegaly on pathogenesis of CMD is not clear.

**Aim**

To assess the effect of somatostatin analogues (SSA) on pathogenesis of carbohydrate metabolism disturbance in acromegaly.

**Patients and methods**

103 acromegaly patients were examined (31 men, 72 women; age 54 (46–61) years; 60 had newly diagnosed acromegaly (NA), 23 receiving SSA, 20 after transphenoidal surgery (TSS)). We analyzed fasting plasma insulin and glucose levels (FPI and FPG), the Matsuda, and HOMA-IR indices, area under insulin curve in the first 30 min (AUCins.30–120), and from 30 to 120 min of oral glucose tolerance test (AUCins.30–120). In 23 NA patients we assessed these parameters after 3 and 6 months of SSA therapy (12 patients) and TSS (11 patients).

**Results**

The prevalence of CMD in NA, SSA, and TSS groups was 52, 87, and 35% respectively. Levels of HOMA-IR index and FPI did not differ between SSA and TSS groups, but were considerably lower compared to the NA group (HOMA-IR 1.7 (IQR 0.7–3.1) vs 3.3 (2.0–7.4), TSS 1.26 mmol/l – in patients with ID genotype, 5.93 ±0.52 mmol/l – in women II genotype. In group I differences in glucose levels reported in patients with II genotype compared to patients with DD and ID genotypes were found to be statistically significant (P<0.05). Other parameters supporting deeper insulin resistance aggravation have been identified prior to delivery only among patients of group I with DD and ID genotypes. Conclusion

**Conclusions**

ACE gene polymorphism determines the risk of PE in pregnant women with T1DM and modulates unfavourable course of the disease, particularly, aggravation of insulin resistance in patients with DD and ID genotypes.

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**EP384**

TRAIL downregulates endothelin 1 and upregulates superoxide dismutase 1 in human aortic endothelial cells under pro-atherogenic conditions

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Introduction

Increased oxidative stress is associated with endothelial dysfunction in atherosclerosis and cardiovascular diseases (CVD). Evidence suggests that tumour necrosis factor-related apoptosis-inducing ligand (TRAIL), a member of the tumour necrosis factor (TNF) superfamily, may also be involved in the pathogenesis of CVD. Observational studies have demonstrated that serum levels of TRAIL are inversely correlated with severity of coronary artery disease. This concurs with other recent in vivo findings suggesting that TRAIL may exhibit vasoprotective effects towards the endothelium, although the mechanism of TRAIL-mediated vasoprotection remains poorly understood. The aim of this study therefore was to characterise the effect of TRAIL on inflammatory gene expression from vascular endothelial cells in vitro under oscillatory flow, an essential component of atherosclerotic plaque formation.

**Methods**

Primary-derived human aortic endothelial cells (HAECs) were exposed to pathological oscillatory shear stress (±10 dynes/cm²) using the BIBD3 solid perfusion unit in the presence and absence of recombinant human TRAIL (100 ng/ml, 24 h). RNA was isolated from the cells using a modified Mirvana method. Gene expression was assessed by a PCR array using qPCR.

**Results**

TRAIL downregulated expression of endothelin 1 (EDN1) gene, which encodes the proinflammatory cytokine EDN1. EDN1 is also associated with reactive oxygen species formation. TRAIL upregulated expression of superoxide dismutase 1 (SOD1) gene, which encodes the potent antioxidant enzyme SOD1.

**Conclusions**

TRAIL exerts an anti-inflammatory effect on the endothelium under pro-atherogenic conditions, at least in part through reduction of oxidative stress.

**Disclosure**

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**EP385**

Surgical trauma and insulin resistance

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**Introduction**

Different surgical procedures are followed by alteration in insulin sensitivity. The aim of our investigation was to analyse the influence of major (open cholecystectomy) and minor surgical stress (laparoscopic cholecystectomy) on insulin resistance.

**Methods**

Insulin resistance was calculated by HOMA-IR before surgery and at 1st, 3rd, and 7th day after the elective operations. All participants were divided in two groups: group A with open cholecystectomy and group B with laparoscopic cholecystectomy. There were no difference between two groups 7 days after surgery (0.78; P>0.05).

**Results**

There were no difference in HOMA-IR between groups A and B before surgery (mean 2.5±0.33 vs 1.99±0.70; P>0.05) as well as the 1st day after surgery (2.55±0.62 vs 1.85±0.58; P>0.05). HOMA-IR was higher in group B 3rd day after operation than in group A (7.56±2.34 vs 2.80±1.78; P<0.05). There was no difference between two groups 7 days after surgery (0.65±0.45 vs 0.74±0.40; P>0.05).

**Conclusion**

Open and laparoscopic cholecystectomy are followed by transient insulin resistance which become normal a week after the operation. Laparoscopic cholecystectomy less deteriorate insulin sensitivity in response to stress than open approach.

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### EP386

**A case of maternally-inherited diabetes with deafness**

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**Introduction**

Maternally-inherited diabetes with deafness (MIDD) is a rare form of monogenic diabetes caused by a point mutation in mitochondrial DNA at a position 3243A>G. The syndrome is characterised by diabetes and sensorineural hearing impairment. Additional clinical features include short stature, cardiomyopathy, myopathy, renal disease, macular dystrophy, and gastrointestinal disease. The majority of patients usually require insulin therapy within 2 years and metformin is probably best avoided because of interference with mitochondrial function. The genetic change is passed down from an affected mother to all her children. However, the clinical phenotype associated with the mutation may be very heterogeneous.

**Case report**

We present a case of a lean 35-year-old female patient who was diagnosed with diabetes at the age of 29 years, suffering from hearing loss and migraine. She tested negative for anti-islet humoral markers (ICA, anti-GAD, and anti-IA2) and her insulin secretory reserve was partially maintained. Four years after the diagnosis, insulin was introduced to therapy. Bilateral neurosensory hearing loss was diagnosed at the age of 29 and required the use of hearing aid. There is a family history of diabetes affecting her mother, maternal uncle, and grandmother.

The clinical suspicion of MIDD was confirmed by the detection of mitochondrial DNA mutation m.3243A>G in patient’s umary epithelial cell DNA sample.

**Conclusion**

It is assumed that MIDD affects up to 1% of all patients with diabetes but often goes unrecognized and is misdiagnosed as either type 1 or type 2 diabetes. Although, it is not possible to predict the likely clinical course associated with this mutation due to variation in phenotype, it is important to suspect and confirm the diagnosis by the genetic testing in order to treat the patient optimally, to screen the patient for other clinical features of the syndrome and to look for the affected family members.

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### EP387

**Association of neutrophil to lymphocyte ratio with different glucose metabolism status**

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**Introduction**

Several studies have shown that prediabetic patients had increased concentrations of inflammatory markers and this association is independent of underlying obesity. Neutrophil to lymphocyte ratio (NLR) is considered as a new inflammatory marker and has been studied extensively in a variety of clinical conditions especially in solid tumours and cardiovascular diseases. Studies evaluating the subclinical inflammation in prediabetes revealed positive association of some inflammatory markers with hyperglycaemia. The aim of this study is to evaluate the association of NLR with different glucose metabolism status groups.

**Methods/design**

The study included 259 patients (213 females, 46 males; mean age 47.4 ± 11.5 and 48.8 ± 15.7 respectively) who admitted to an Out-Patient Endocrinology Clinic of a State Hospital in Turkey. The asymptomatic adults were classified in three groups as normal glucose metabolism, impaired fasting glucose, and diabetes. The asymptomatic adults were classified in three groups as normal glucose metabolism, impaired fasting glucose, and diabetes.

**Results**

There were statistically significant differences between groups in terms of fasting glucose and HOMA-IR levels as expected (P < 0.000 and P = 0.047 respectively). Otherwise there are no differences in terms of BMI, insulin, lipids, and NLR.

### EP388

**Contribution of glucose variability to HbA1c levels in patients with type 1 diabetes**

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**Background**

Optimal management of type 1 diabetes requires full understanding of the relationships between the triad: HbA1c, fasting plasma glucose, and glucose variability (GV). As GV may contribute to HbA1c we assessed the influence of GV in HbA1c levels.

**Research design and methods**

We retrospectively analysed 9393 h of continuous glucose monitorings (CGMs) from 61 patients with type 1 diabetes. Periods of 24 h with missing values were excluded. We calculated various measures of GV and used a regression model to determine the impact of each GV measure to HbA1c level. GV was calculated using EasyGV Software and CGMs were recorded using iPro2 (Medtronic, Northridge, CA, USA).

**Results**

A total of 9393 h of CGM were analysed. Mean duration of diabetes was 17.7 ± 9.6 years and HbA1c was 7.9 ± 1.1%, s.d., continuous overlapping net glycaemic action (CONGA), mean absolute glucose (MAG), and mean of daily differences (MODD), were positively correlated with HbA1c (correlation coefficient of 0.26, 0.37, 0.26, and 0.33, respectively, all P < 0.05), and all measures of GV were significantly higher for higher values of HbA1c (< 7, 7.8–8, 8–9, and > 9%), all P < 0.05). Intraday variability, measured by MODD, accounted for 13.1% of HbA1c. Furthermore, MODD was positively correlated with measures of quality of glycemic control, like glycemic risk assessment in diabetes equation (GRADE) score, J-index, high blood glucose index (HBGI), M-value, and average daily risk ratio (ADDR) (correlation coefficient of 0.41, 0.54, 0.57, 0.54, and 0.80, respectively, all P < 0.05).

**Conclusion**

GV contributes significantly to HbA1c levels. This effect is more pronounced at higher HbA1c levels. Intraday variability was the most important contributor to HbA1c. GV impairs significantly the quality of glycemic control of type 1 diabetic patients.

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### EP389

**Increasing NAD11 availability in skeletal muscle to augment energy metabolism**

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NAD^+, an essential coenzyme in energy production, has recently risen to prominence as a signalling molecule central in modulating cellular metabolism and mitochondrial function. NAD^+ dependent protein deacetylase sirtuin (SIRT) proteins regulate key metabolic transcription factors, including FOXOs and PGC-1alpha in muscle, in response to cellular energy demands and metabolic stress. Declining NAD^+ metabolic and mitochondrial function are hallmark features of many patho-physiological processes such as ageing and type 2 diabetes. Thus, boosting NAD^+ availability may have beneficial and therapeutic potential. NAD^+ consumption (e.g. SIRTs) requires its re-synthesis through precursor salvage to maintain appropriate levels. Here we further define a skeletal muscle specific pathway to NAD^+ and energy metabolism. Through mRNA and protein expression analysis of NAD^+ biosynthesis genes we show that skeletal muscle relies on a limited set of salvage enzymes for NAD^+ biosynthesis and replenishment. The most highly expressed and skeletal muscle specific of which is nicotinamide riboside kinase 2 (Nmrk2), which salvages the NAD^+ precursor molecule nicotinamide riboside (NR) to produce NAD^+. Nmrk2 demonstrates muscle fibre type specificity, being fivefold enriched in type II fibres compared to type I. Nmrk2 expression is induced during mouse myotube differentiation and embryonic muscle development in zebrafish. Primary derived mouse muscle cells supplemented with 0.5 mM NR for 24 h showed a significant 30% increase (P<0.001) in NAD^+ levels with unchanged NADH, suggesting a shift in the redox ratio in favour of the oxidised form. Moreover, oxygen consumption rate was increased by 20% in NR treated myotubes when assessed in muscle, in response to cellular energy demands and metabolic stress. Declining NAD^+ metabolic and mitochondrial function are hallmark features of many patho-physiological processes such as ageing and type 2 diabetes. Thus, boosting NAD^+ availability may have beneficial and therapeutic potential. NAD^+ consumption (e.g. SIRTs) requires its re-synthesis through precursor salvage to maintain appropriate levels. Here we further define a skeletal muscle specific pathway to NAD^+ and energy metabolism. Through mRNA and protein expression analysis of NAD^+ biosynthesis genes we show that skeletal muscle relies on a limited set of salvage enzymes for NAD^+ biosynthesis and replenishment. The most highly expressed and skeletal muscle specific of which is nicotinamide riboside kinase 2 (Nmrk2), which salvages the NAD^+ precursor molecule nicotinamide riboside (NR) to produce NAD^+. Nmrk2 demonstrates muscle fibre type specificity, being fivefold enriched in type II fibres compared to type I. Nmrk2 expression is induced during mouse myotube differentiation and embryonic muscle development in zebrafish. Primary derived mouse muscle cells supplemented with 0.5 mM NR for 24 h showed a significant 30% increase (P<0.001) in NAD^+ levels with unchanged NADH, suggesting a shift in the redox ratio in favour of the oxidised form. Moreover, oxygen consumption rate was increased by 20% in NR treated myotubes when assessed using a Seahorse extracellular flux analyser, indicating that the NR is enhancing mitochondrial respiration as a result of boosting cellular NAD^+ availability. Our data provides evidence that Nmrk2 is important for skeletal muscle NAD^+ bioavailability and highlights the therapeutic potential for NR supplementation to target mitochondrial function in skeletal muscle.

Disclosure
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EP390

Prepregnancy care: an opportunity not to be missed
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Introduction
Our aim was to evaluate the effectiveness of a regional prepregnancy care (PPC) programme for women with both type 1 and 2 diabetes. Methods
This prospective cohort study included women with pregestational diabetes attending five antenatal centres in the West of Ireland between January 2006 and December 2013. Comparisons were made between those that did and did not attend the PPC programme. Primary outcomes included composite adverse neonatal outcome (shoulder dystocia, congenital malformation, stillbirth, or neonatal death), macrosomia, caesarean delivery, admission to neonatal care unit, per trimester Hba1c, and prepregnancy folic acid use.

Results
In total 452 women were included, 275 (60.8%) with type 1 diabetes and 177 (39.2%) with type 2 diabetes. PPC was attended by 148 (32.7%) women. Those who attended PPC were healthier at baseline with 54.9% vs 96.6% without PPC achieving prepregnancy folic acid levels (P<0.01), as was the mean second trimester HbA1c (6.6% vs 6.2%, P<0.01). Mean first trimester HbA1c was lower in patients who attended PPC (5.6% vs 7.8%, P<0.01), as was the mean second trimester HbA1c (6.6% vs 6.2%, P<0.01).

There was no significant difference in third trimester Hba1c between groups. Rates of adverse neonatal outcomes were higher in those that did not attend PPC (9.5% vs 4.1%, P=0.04). A lower proportion of infants born to women who attended PPC required neonatal unit admission (37.2% vs 48.7%, P=0.02). There was no difference in rates of caesarean delivery or macrosomia between groups. Binary logistic regression analysis identified that attendance at PPC independently reduced the odds of a serious adverse neonatal outcome (aOR 0.27, CI 0.09–0.83, P=0.02).

Conclusion
These findings suggest that provision of a regional PPC programme confers both an individual and economic benefit and should be available to all women with pregestational diabetes.

Disclosure
This work was supported by the Health Research Board of Ireland.

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EP391

Lipoprotein associated phospholipase A2 was not associated with diabetic retinopathy
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Aim
Diabetic retinopathy is an important microvascular complication in diabetic patients. The association between hyperlipidemia and diabetic retinopathy remains elusive. Lipoprotein associated phospholipase A2 (Lp-PLA2) is a Ca-independent serine kinase that hydrolyses oxidized LDL and forms lysophosphatidylcholine and free fatty acid. The aim of the study was to determine serum levels of Lp-PLA2, traditional lipids, apolipoproteins in patients with diabetic retinopathy and to evaluate correlation of these parameters with disease severity.

Methods
A total of 67 diabetic patients were divided into three groups (nonprogressive diabetic retinopathy, proliferative retinopathy, and no retinopathy) based on fundoscopic examination and matched to 15 healthy and non-diabetic people. Blood samples for lipids, apolipoproteins, Lp-PLA2 were drawn.

Results
No significant difference was observed in terms of total cholesterol, TG, LDL-C levels between groups. However HDL-C levels were similar in proliferative diabetic retinopathy, nonproliferative retinopathy patients and diabetic controls (42.5±6.4, 46.8±12.3) and were lower than healthy controls (61.2±14.5, P<0.005). No statistically significant difference was shown with respect to apolipoprotein A1, apolipoprotein B, apo B: apo A1 ratio in all comparisons.

Conclusions
Serum levels of lipids, apolipoproteins and Lp-PLA2 were not associated with diabetic retinopathy. Although, Lp-PLA2 were found to be associated with macrovascular complications of diabetes in most studies, the role of this molecule in microvascular complications wasn’t known. The larger sample sized studies may clarify the relationship between Lp-PLA2 and retinopathy.

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EP392

Concentrations of the vitamin D metabolite 1,25(OH)2D and its relationship to inflammatory and metabolic parameters in diabetes type 2
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Background
While 25-hydroxy-vitamin D (25(OH)D) has been thoroughly investigated, the role of active vitamin D metabolite 1,25(OH)2D in a metabolic syndrome still remains unclear. The aim of our study was to determine the association between 25(OH)D and 1,25(OH)2D levels and several metabolic parameters and inflammatory markers in postmenopausal women with diabetes type 2 (T2DM).

Methods
Anthropometric variables, serum 25(OH)D, 1,25(OH)2D, C-reactive protein (CRP), fibrinogen, PAI-1, fasting glucose, fasting insulin, and Hba1c were measured in 125 postmenopausal women with T2DM. Insulin resistance was estimated by homeostasis model assessment (HOMA-IR) and β-cell function by HOMA-B. A total of 125 diabetic patients were divided by BMI in normal weight group (n=22, BMI 22.7±1.5 kg/m2) and adipose group (n=93, BMI 32.2±5.8 kg/m2). Control group consisted of healthy obese postmenopausal women (n=46, BMI 34.9±6 kg/m2).

Results
Serum 25(OH)D concentrations were highest in the lean diabetics compared with obese diabetics and control subjects (P<0.0007) and were significantly associated with fasting glucose, insulin, HOMA-B, BMI, and PAI-1. In diabetic patients 25(OH)D levels were positively associated with HDLC (P<0.001) and negatively with triglycericeter (P<0.01) and PAI-1 (P<0.001). Serum 1,25(OH)2D concentrations were significantly higher in control obese subjects (77.4±17.0 nmol/l) compared with adipose diabetics (P<0.001), with no difference in relation to lean diabetics. Fasting glucose and Hba1c negatively correlated (P<0.01), whereas cholesterol and LDL-C positively correlated (P<0.001) and HDLC was negatively correlated (P<0.05).

Disclosure
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(P<0.01) with 1,25(OH)2D. Furthermore, 25(OH)D correlated with PAI-1 in all subjects while 1,25(OH)2D correlated with fibrinogen but only in obese control subjects.

Conclusions
In T2DM women low serum 25(OH)D and 1,25(OH)2D levels were associated with atherogenic dyslipidemia, glucose parameters, and low grade inflammation. The active hormonal form of vitamin D, 1,25(OH)2D correlated with cholesterol, LDL-C, and fibrinogen, while 25(OH)D correlated with triglycerides, HDL-C, and PAI-1, suggesting that there may be an independent mechanism of action for 1,25(OH)2D in relation to metabolic dysregulation.

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EP393

Abstract unavailable.
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EP394

10 years of improving outcomes for women with pre-gestational diabetes
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Pregnancy for women with type 1 or type 2 diabetes is a high-risk time. The Atlantic diabetes in pregnancy (DIP) programme aims to provide coordinated, optimal evidence-based clinical care for women with diabetes over five hospital centres in the West of Ireland. After previously auditing pregnancy outcomes in 2008 and again in 2011 we now look at our 10-year outcomes. Changes in clinical care delivery that have occurred over that time include; the provision of dedicated combined antenatal/diabetes clinics, pre-pregnancy care clinics delivered by specialist diabetes and obstetric staff, use of a diabetes electronic management system, use of locally developed clinical care guidelines and professional and patient education materials. We examined outcomes in 440 pregnancies, divided into groups in groups of pre- and post-audit cycles, after which further change was implemented (2005 – 2008, 2009 – 2011, and 2012–2014). We saw a trend towards reduction in a lot of major outcomes. This is despite an increase in maternal age, maternal weight/BMI and a significant increase in numbers of women obese at the start of pregnancy. There has been an overall significant reduction in gestational weight gain. There has not however been a reduction amongst overweight women, just obese and normal weight women. We also saw an increase in attendance at pre-pregnancy care and a reduction in mean HbA1c values. There has been a significant reduction in congenital malformations and a non-significant reduction in large for gestational age babies, birth weight, smoking, neonatal hypoglycaemia, jaundice and admissions to the neonatal intensive care unit.

Conclusion
Changing the process of clinical care delivery can improve outcomes in women with pregestational diabetes. We now need to target women prior to pregnancy in order to optimise BMI.

Disclosure
Health Research Board of Ireland.
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EP395

Unawareness hypoglycaemia in patients with type 1 diabetes mellitus: prevalence and predictive clinical characteristics
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Background
The prevalence of unawareness hypoglycaemia in patients with type 1 diabetes mellitus (T1DM) is uncertain. This study aims to determine its prevalence and predictive clinical characteristics with greater precision.

Methods
Prospective study. 128 patients were recruited between September 2013 and January 2014. Awareness of hypoglycaemia was assessed using the ‘Clarke’ questionnaire and was classified into two groups, depending on the presence (group 1) or absence (group 2) of symptoms perception.

Results
The ‘Clarke’ questionnaire was completed by 128 patients with T1DM: 53.8% females; mean age 36.2±12.8 years; duration of diabetes 15.65±9.18 years; HbA1c 7.45±1.35%; 87.5% used intensive insulin therapy with multiple insulin doses. 80 patients (62.5%) were included in group 1 and 48 (37.5%) in group 2. The frequency of at least one episode of severe hypoglycaemia during the previous year was 20.3% in group 1 and 37.5% in group 2. 43% of patients in group 1 and 56.3% in group 2 needed a blood glucose value <50 mg/ml to notice symptoms. 43% of patients in group 1 and 66.7% in group 2 considered their symptoms hardly ever or never warned them about the presence of hypoglycaemia. There have not been any significant differences between both groups in diabetic microangiopathy, duration of disease, eating disturbances and insulin regimens (basal-bolus vs biphasic).

Conclusions
We have observed a high prevalence of unawareness hypoglycaemia in patients with T1DM. Educational strategies are needed to improve their perception of hypoglycaemia symptoms.

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EP396

Glycaemic control is comparable in patients with or without significant hepatic fibrosis as assessed by NAFLD fibrosis score
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Background and aims
Non-alcohol fatty liver disease (NAFLD) is increasingly recognised in diabetic patients with metabolic syndrome. Patients with poorly-controlled diabetes and metabolic syndrome are likely to have significant liver inflammation leading to fibrosis. NAFLD fibrosis score (NFS) is a validated non-invasive scoring system that identifies liver fibrosis in patients with NAFLD. The aim of this study is to examine the glycaemic control in patients with or without significant hepatic fibrosis as assessed by NFS in routine clinical practice.

Methods
All patients with type 2 diabetes or impaired glucose tolerance/fasting glucose, attending the diabetic clinic from March to June 2014 were included retrospectively. Patients with type 1 diabetes and gestational diabetes were excluded. Data were obtained from laboratory database and electronic patient record (Cellma). NFS was calculated for each patient based on age, BMI, laboratory data were studied. In our cohort of 153 patients, 64.1% (98) of patients had significant fibrosis with a median score of 1.169 (0.898–1.563) while the rest of the patients were indeterminate (66.0%, n=101) or had no significant fibrosis (9.8%, n=15).

The median BMI for patients with significant hepatic fibrosis was 30.0 (27.8–34.5) kg/m² while for patients without significant fibrosis (including indeterminate) the median BMI was 34.5 (30.3–43.2) kg/m² (Z = 0.639).

Glycaemic control is comparable in patients with or without significant hepatic fibrosis (group 1) or absence (group 2) of symptoms perception.

Results
521 patients were screened and only 29.4% (153) of patients with complete laboratory data were studied. In our cohort of 153 patients, 64.1% (98) of patients were male and the median age was 63 (IQR 56.0–71.5) years. Using the NAFLD fibrosis score, almost a quarter of our patients (24.2%, n = 37) had significant fibrosis with a median score of 1.169 (0.898–1.563) while the rest of the patients were indeterminate (66.0%, n = 101) or had no significant fibrosis (9.8%, n = 15).

The median BMI for patients with significant hepatic fibrosis was 30.0 (27.8–34.5) kg/m² while for patients without significant fibrosis (including indeterminate score based on NFS), the median BMI was 34.8 (30.3–43.2) kg/m² (P < 0.001).

Interestingly, there were no significant differences in the mean HbA1c readings in patients with or without significant hepatic fibrosis (35.2±15.3 mmol/mol vs 56.6±17.9 mmol/mol, P = 0.639).

Conclusion
In conclusion, we did not observe any significant differences in glycaemic control in patients with or without significant hepatic fibrosis, as assessed by NAFLD fibrosis score.

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Patients, especially children, with type 1 diabetes (T1D) have an increased risk of developing other autoimmune disorders including coeliac disease (CD). While the general population prevalence of CD is ~1%, in patients with T1DM the prevalence of CD is higher (0.6-10%). Gluten free diet (GFD) imposes limitations in dietary options. Many of the gluten-free foods have a high glycemic index. This can influence glycemic values and metabolic parameters. We selected the subgroup of pts with T1D attending our service between June 2011 and June 2013 who have concomitant CD (n=30). To determine whether differences exist in their metabolic parameters compared to those of the total cohort of patients with T1D attending our service in the same time period (n=905), we did a cross-sectional analysis of clinic measurements of weight, BMI, BP, HbA1c, lipid profiles, albumin creatinine ratios, and tissue transglutaminase IgG antibody titres (TTG) (as a marker of adherence to a GFD). The CD+T1D group consisted of 18 (60%) females and 25 (83%) adults (>18 years) and had a mean age of 37 (s.d. 19). The T1D group consisted of 431 (48%) females and 798 (88%) adults (>18 years) and had a mean age of 37 (17). HbA1c in the CD+T1D group was 76.4 mmol/mol (s.d. 17.4) vs 70.3 (17.7) in the T1D group (P=0.004). Children overall had higher HbA1c values (83.6 and 75.7, P<0.05). In the CD+T1D group, lipid profiles showed lower total cholesterol (4.0 vs 4.6), LDL cholesterol (2.0 vs 2.4), triglycerides (1.0 vs 1.3), and higher HDL cholesterol (2.0 vs 1.7) mmol/l levels than the T1D group (P<0.003). There was no significant difference in the proportion taking cholesterol lowering drugs (35% vs 31%). The CD+T1D group had a lower average BMI (24.0 vs 26.4, P<0.004). CD+T1D presents a challenge to achieving target HbA1c but confers some benefits for lipid profiles. doi: 10.1530/endoabs.37.EP397

EP398

Modulation of metabolic parameters and antioxidant enzymes in diabetic ageing rat brains: beneficial role of metformin
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Objective The objective of this study was to investigate beneficial effects of metformin on membrane bound enzymes (monooamine oxidase, Na⁺K⁺ ATPase) and antioxidant enzymes (superoxide dismutase and glutathione S-transferases), lipid peroxidation, neurolipofuscin, and DNA degradation in diabetic aging female rats.

Methods Young (5 months) adult (12 months) and aged (24 months) rats will be diabetic by using alloxa monohydrate. Metformin was administered i.p. at a dose of 200 mg/kg per day for 30 days to both control and diabetic aging rats. Learning was tested in a Morris water maze. A detailed study was carried on membrane linked enzymes, membrane fluidity, neuropilofuscin, antioxidant enzymes, and DNA degradation to identify the antiabetica and antiaging role of metformin using biochemical, molecular, and histochemical study.

Results Present study shows that there was a similar pattern of increased lipid peroxidation, neurolipofuscin, DNA degradation, and monoamine oxidase activity and a decrease in membrane fluidity, Na⁺K⁺ ATPase, antioxidant enzymes activities in both aging and diabetes. Metformin was found to be an effective treatment in stabilizing and normalizing the membrane functions; therefore this therapy can be considered an alternative to be explored further as a means of diabetic and aged related disorders control. Metformin treatment also helped to reverse the age-related changes studied, to normal levels, elucidating an anti-aging, antiabetica, and neuroprotective action.

Conclusions The results of this study will be useful for pharmacological modification of the aging process and applying new strategies for control of age-related disorders including metabolic syndrome.

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EP397

Targeting optimal metabolic parameters in type 1 diabetes and concomitant coeliac disease: an extra challenge
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EP399

Diabetes (complications & therapy)

EP400

Efficacy of sitagliptin added on to intensive insulin therapy in type 2 diabetic patients
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Aim Despite multiple dose injections some patients still fail achieving HbA1c target. We aimed to evaluate the effect of sitagliptin add on therapy to multiple dose insulin injections.

Method Data of 47 (seven males and 40 females) type 2 diabetic patients who had HbA1c over 7% were retrospectively evaluated. They were already treated with premix lispro or aspart insulin (n=28), glargine plus premal regular or aspart or lispro insulin (n=15), and detemir plus premal aspart insulin (n=2), and glargine plus premix Lispro insulin (n=2) for at least 3 months before sitagliptin add on therapy. The insulin scheme was intensified (glargine plus premal regular or aspart or lispro insulin (n=32), and detemir plus premal aspart aspart insulin (n=2), and NPH (twice daily regular or lispro insulin (n=13)).

Results The patients were aged 56.26±8.69 years. Mean duration of diabetes was 14.41±7.57 years. Mean BMI 37.75±6.08 kg/m² (28.81–53.78 kg/m²). One patient had sleeve gastroctomy and still continued sitagliptin afterwards. Duration of insulin therapy before sitagliptin therapy ranged between 3 months and 22 years. Before sitagliptin therapy total daily dose was 91.13±32.22 units (32–204 units) (n=46), HbA1c level within 6 months preceding sitagliptin therapy was 9.65±1.70% (7.25–14.3%) and duration of sitagliptin therapy ranged between 1 and 25 months. The patients who used sitagliptin in <6 months were the ones who were lost follow-up. Neither of them discontinued sitagliptin due to side effects. Weight change was 3.01 (gain) ±3.47 kg (~2.30 to 15.00). Only 43 had follow-up total daily insulin dose data. Mean change was 20.72 units increment ±29.86 (~48 to 90 units). According to the available follow-up records, mean HbA1c change was 0.95 ±1.48% (~4.32 to 25.8%). When data of the patient who had undergone sleeve gastroctomy was deleted, mean weight change was 2.63 (gain) ±2.74 kg (~2.30 to 6.60). Mean total daily insulin dose change was 23.90 units increment ±30.68 (~48 to 90 units). Mean HbA1c change did not differ significantly (0.93 ±1.48%; range: ~4.32 to 25.8%). HbA1c change was correlated neither with total daily insulin dose change nor with weight change.
Research design and methods
Diabetes control and anthropometric data of 94 children with type 1 diabetes who were on continuous s.c. insulin therapy using insulin pump were compared with those for 40 children with type 1 diabetes mellitus who were on multiple injections using basal insulin (Lantus) and prandial insulin (Novo-rapid) (three to four shots/day) for more than 2 years. Mean HbA1c, mean blood glucose (MBG), hypoglycemia and DKA frequency were recorded.

Results
Patients using pump therapy were older than patients on pen injections. However, the duration of diabetes did not differ between the two groups. Patients on CSII had significantly lower HbA1c, MBG, and insulin dose/kg compared with children using insulin pens. The frequency of severe hypoglycemia, ketoacidosis, or hospitalization was similar between groups at this time period. The majority (90/94) of patients on CSII expressed their desire to continue on CSII and appreciated its value as easier way to adjust insulin dose to their variable daily requirements.

Discussion
CSII is safe and well tolerated in young children with diabetes and may have positive effects on QOL. In addition, CSII improved diabetes control using less insulin/kg compared with pen injections. However, children on CSII had higher weight gain and BMI.

Conclusion
Our data indicate that CSII is safe and well tolerated in this population. The proper use of CSII in children with type 1 diabetes mellitus appears to improve glycemic control using less s.c. insulin/kg per day and their quality of life. However, excessive weight gain should be avoided.

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**EP402**

**Is vitamin D a predictor of premature atherosclerosis in type 2 diabetic patients?**

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Introduction
A poor vitamin D status has been related to an increased risk of cardiovascular disease. Carotid intima–media thickness (IMT) has shown to be an early marker of subclinical atherosclerotic Therefore, we aimed at examining the association between vitamin D status and the extent of carotid IMT in type 2 diabetics.

Subjects and methods
In a cross sectional study 78 type 2 diabetic patients attending the Diabetes and Endocrinology Clinic in Kasr El Aini Hospital were subjected to: full history, physical examination, anthropometric measurements (BMI and waist circumference), fasting glucose, HOMAIR, serum cholesterol, triglycerides, LDL, HDL, 25(OH) vitamin D, and carotid Doppler.

Results
Diabetics with normal CIMT (n=26) all with sufficient vitamin D, diabetic with increased CIMT (n=52) (40 sufficient 76.9% and 12 insufficient 23.1%). Six patients with increased CIMT had carotid plaque. Only one patient had vitamin D insufficiency, all other five patients had sufficient vitamin D. Vitamin D negatively correlated with Rt IMT, however, not statistically significant (r=-0.003, P=0.981). Negative correlation between fasting blood glucose and vitamin D statistically significant (r=-0.415, P<0.001). Negative correlation between cholesterol and Rt intima (r=-0.340, P=0.002).

Conclusion
Low serum 25(OH)D has no consistent association with mean IMT. Thus could not predict subclinical atherosclerosis in diabetics, the contribution of the local activated vitamin D system within atherosclerotic plaque has not been appropriately investigated yet. Therefore, both basic research studies and clinical trials are needed for better elucidating the therapeutic and path physiological role of vitamin D in atherogenesis and CV diseases.

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**EP403**

**Long-term use of insulin pump vs pens in treating young children with type 1 diabetes**

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Introduction
Unequivocal evidence for the benefit of MDI, the analogs and CSII-treatment in children is lacking. This study assesses the effects of insulin pump (CSII) vs pens in treating children with type 1 diabetes for more than 2 years.

**EP404**

**Effect of liraglutide 1.8 mg in patients with non-controlled type 2 diabetes mellitus at an endocrinology clinic: LIED-2 Study**

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Background and aims
To describe the characteristics of patients with non-controlled type 2 diabetes mellitus with liraglutide treatment.

Materials and methods
Retrospective descriptive study. 85 outpatients (women 49, ages 18–86 years old with non-controlled type 2 diabetes mellitus were evaluated between July 2013 and March 2014 and received treatment with liraglutide 1.8 mg Q18/day (0.6 mg Q18 during the first week, 1.2 mg Q18 during the second week and 1.8 mg during the third week and the rest of the treatment). Age, sex, diagnosis time, weight, HbA1c, fasting glucose, systolic and diastolic blood pressure, pharmacological treatment during 6 months were extracted for analysis.

Results
Patients treated with liraglutide 1.8 mg as monotherapy or in conjunction with a therapeutic scheme decreased HbA1c values at 3 and 6 months (1.02% 95% CI ± 0.93 P<0.0001 y 2.08% 95% CI ± 0.8 P<0.0001); fasting glucose at 3 and 6 months (37 mg/dl 95% CI ± 33 P<0.0001 y 68 mg/dl 95% CI ±26 P<0.0001); weight at 3 and 6 months (3 kg 95% CI ±10 P<0.0001 y 5 kg 95% CI ±10 P<0.0001); SBP at 3 and 6 months (9 mmHg 95% CI ±15 P<0.0001 y 16 mmHg 95% CI ±16 P<0.0001); DBP at 3 and 6 months (3 mmHg 95% CI ±6 P<0.0001 y 6 mmHg 95% CI ±6 P<0.0002). 40% of patients reached HbA1c <7.0%: 20% reduction in HbA1c, 39% reduction in fasting blood glucose, 6% reduction in mean weight (1–18%, 1–12 kg), 95% reached SBP <140 mmHg; 100% reached DBP <90 mmHg. Reported adverse events during treatment were nausea (27%), abdominal pain (18%), hypoglycemia (14%), diarrhea (9%), respiratory symptoms (7%). Metformin was present in 65% cases of nausea, 55% cases of diarrhea and 43% of cases of abdominal pain. No fatal adverse events occurred.

Conclusion
Patients treated with liraglutide 1.8 mgQ18/day in monotherapy or in conjunction with a therapeutic scheme showed a decrease in HbA1c, fasting glucose, weight, SBP, DBP during a 6 month treatment.

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EP406
The frequency of fall and risk factors in elderly patients with type 2 diabetes
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The aims of the study were to determine the frequency of falls in elderly patients with type 2 diabetes mellitus and to evaluate the risk factors for falls. In the study, 100 (mean age 64.9±11.0 years) (65 females, 35 males) elderly patients with type 2 DM were enrolled. Medical record abstraction of sociodemographic, with type 2 diabetes mellitus and to evaluate the risk factors for falls. In the study, 100 newly diagnosed normotensive type 2 diabetes mellitus patients between 30 and 60 years of age were enrolled from endocrine OPD of a tertiary care centre during a period of 1 year. All cases were subjected to thorough clinical history, examination and 2D echocardiography along with HbA1c.

Observations and results
Out of 100 patients of newly diagnosed normotensive type 2 DM; 41% patients had LVDD and 37% patients had LVH. The mean HbA1c of population with LVDD was 7.67±0.90% and that with LVH was 7.74±0.91%. The LVDD and LVH were positively correlated with HbA1c (P value = 0.0057 and 0.0011) respectively.

Conclusion
LVDD and LVH were positively correlated with HbA1c in newly diagnosed T2DM population.

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EP407
Factors influencing prognosis in patients hospitalised with diabetic ketoacidosis
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Background
Diabetic ketoacidosis is characterised by biochemical tired of hyperglycemia, acidosis, and ketonemia. It remains a life threatening condition despite improvement in diabetic care, timely identification and intervention remains the backbone of treatment.

Aim and objectives
i) To evaluate the clinical and biochemical prognostic markers in diabetic ketoacidosis. ii) To correlate the various prognostic markers with mortality in diabetic ketoacidosis.

Settings and design
A prospective multicenteric observational study done at tertiary care centre.

Methods and materials
Two hundred and seventy patients hospitalised with diabetic ketoacidosis over a period of 1 year were evaluated clinically and by laboratory tests. Serum assays of serum electrolytes, glucose and blood pH, and clinical outcome of either discharge home or death were evaluated.

Statistical analysis
Data were analysed by SPSS version 17 and was presented in the values of mean, median, and percentages. The P value of <0.05 was considered significant.

Results
The significant predictors of final outcome obtained were further regressed together and subjected with multivariate logistic regression (MLR) analysis. The MLR analysis further revealed that the male sex had 7.93-fold higher favourable outcome as compared to female sex (OR=7.93, 95% CI 3.99–13.51) while decrease in mean APACHE II score (14.83) and S. PO2 (43.8) at presentation may lead 2.86 (OR = 2.86, 95% CI 1.72–7.03) and 2.71 (OR = 2.71, 95% CI 1.51–6.99) fold better favourable outcome respectively as compared with higher levels (APACHE II score: 25.00; S. PO2: 6.04).

Conclusions
Sex, baseline biochemical parameters like APACHE II score, and phosphate level, were important predictor of mortality from DKA.

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EP408
Microalbuminuria in children and adolescents with type 1 diabetes mellitus: predictive factors
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Objective
Microalbuminuria is usually the first microvascular complication of type 1 diabetes mellitus (T1DM). We aimed to identify its frequency, time of occurrence and related risk factors.

Methods
Clinical reports of 201 children followed in our institution were retrospectively analysed (diabetes duration 3.8±3.6 years, age at diagnosis 8.1±3.7 years, HbA1c value 9.0±1.7%). Statistical analysis was performed with SPSS version21 for Windows. Results are expressed in frequencies and means ± S.D.

Statistical significance was considered as P value <0.05.

Results
Seventeen (ten females; seven males) patients (8.5%) presented microalbuminuria in a mean time of 5.5±5.8 years: five children (29.4%) 2 years after diabetes onset and nine children (52.9%) 5 years after it (four children between 2 and 5 years of diabetes duration). In the logistic regression analysis, longer diabetes duration (6.3±3.7 years vs 3.5±3.5 years, P = 0.005, OR = 1.38), higher total cholesterol (TC) (180.6±57.5 mg/dl vs 159.1±31.0 mg/dl, P = 0.03, OR = 1.26), higher LDL (125.5±36.3 mg/dl vs 110.9±24.7 mg/dl, P = 0.04, Diabetic ketoacidosis is characterised by biochemical tired of hyperglycemia, acidosis, and ketonemia. It remains a life threatening condition despite improvement in diabetic care, timely identification and intervention remains the backbone of treatment.

Aim and objectives
i) To evaluate the clinical and biochemical prognostic markers in diabetic ketoacidosis. ii) To correlate the various prognostic markers with mortality in diabetic ketoacidosis.

Settings and design
A prospective multicenteric observational study done at tertiary care centre.

Methods and materials
Two hundred and seventy patients hospitalised with diabetic ketoacidosis over a period of 1 year were evaluated clinically and by laboratory tests. Serum assays of serum electrolytes, glucose and blood pH, and clinical outcome of either discharge home or death were evaluated.

Statistical analysis
Data were analysed by SPSS version 17 and were presented in the values of mean, median, and percentages. The P value of <0.05 was considered significant.

Results
The significant predictors of final outcome obtained were further regressed together and subjected with multivariate logistic regression (MLR) analysis. The MLR analysis further revealed that the male sex had 7.93-fold higher favourable outcome as compared to female sex (OR=7.93, 95% CI 3.99–13.51) while decrease in mean APACHE II score (14.83) and S. PO2 (43.8) at presentation may lead 2.86 (OR = 2.86, 95% CI 1.72–7.03) and 2.71 (OR = 2.71, 95% CI 1.51–6.99) fold better favourable outcome respectively as compared with higher levels (APACHE II score: 25.00; S. PO2: 6.04).

Conclusions
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EP408
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Results
Seventeen (ten females; seven males) patients (8.5%) presented microalbuminuria in a mean time of 5.5±5.8 years: five children (29.4%) 2 years after diabetes onset and nine children (52.9%) 5 years after it (four children between 2 and 5 years of diabetes duration). In the logistic regression analysis, longer diabetes duration (6.3±3.7 years vs 3.5±3.5 years, P = 0.005, OR = 1.38), higher total cholesterol (TC) (180.6±57.5 mg/dl vs 159.1±31.0 mg/dl, P = 0.03, OR = 1.26), higher LDL (125.5±36.3 mg/dl vs 110.9±24.7 mg/dl, P = 0.04,
Introduction
Atherosclerotic complications are the leading causes of morbidity and mortality among patients with DT2.

Aim
To investigate the possible role of dyslipidaemia, hypertension and chronic kidney disease (CKD) on the characteristics of carotid atherosclerosis (presence of plaque, carotid IMT and total plaque area) in patients with DT2.

Material and methods
Patients aged 60–75 years with DT2 were included in this study. Control group included 24 healthy subjects the same age. Other atherosclerosis risk factors of subjects, including smoking, hypertension, dyslipidaemia, and CKD, were identified with a questionnaire and a blood test. The IMT was measured using automated edge detection software as the distance between the lumen–intima interface and the media–adventitia interface. Atherosclerotic plaque was defined as a focal structure encroaching into the arterial lumen of 0.5 mm or 50% of the surrounding IMT value or IMT of >1.5 mm. Total plaque area (TPA) was calculated as the sum of all plaque areas.

Results
We divided all patients (DT2 and control) into three groups: Group 1 (n = 24) – patients did not have any additional atherosclerosis risk factor, Group 2 (n = 25) – patients had one additional atherosclerosis risk factor, and Group 3 (n = 43) – patients had two or three additional atherosclerosis risk factors. Using multiple linear regression analysis adjusted for confounding factors, IMT and TPA were significantly correlated with age > 60 years (β = 0.359, P < 0.0001; β = 0.263, P = 0.0001), hypertension (β = 0.041, P = 0.003; β = 0.126, P < 0.0001), dyslipidaemia (β = 0.066, P < 0.0001; β = 0.125, P < 0.0001) and CKD (β = 0.054, P = 0.003; β = 0.165, P < 0.0001), respectively. However, gender (men) was not significantly correlated with IMT (P = 0.171) and TPA (P = 0.112).

Conclusion
The presence of dyslipidaemia, hypertension, and different CKD status were predictors of carotid plaque.

EP411
Validation of self-reported oral health measures for predicting periodontitis among adult Filipinos with type 2 diabetes mellitus
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Diabetes mellitus is currently being recognised as a global health problem. The likelihood of periodontal disease among diabetics is thrice and progresses rapidly when uncontrolled. Diabetics were less likely to see a dentist than to seek consultation with a doctor for diabetes care. A cheap and easy way of clinical assessment via self-reported oral health questionnaire would be of great use especially in a developing country like The Philippines. This study aims to validate self-reported oral health measures, socio-demographic and medical variables in predicting the severity of periodontitis in Filipino adults with type 2 diabetes. The validated self-reported oral health questionnaires created by the CDC Periodontal Disease Surveillance Project was translated into Filipino and used. A cross-sectional study of 180 participants was conducted in a single institution. Multivariable logistic regression analyses was used to determine significant predictors of serious periodontitis. Socio-demographic and medical variables considered to be significantly predictive of serious periodontitis were male sex (OR = 2.17), low educational status (OR = 2.98), poor glycaemic control (OR = 2.58), less frequent dental visits (OR = 2.77) and teeth loss > 6 (OR = 5.02). Self reported oral health variables shown to be significantly predictive of serious periodontitis included gum disease – Q1 (OR = 8.33), state of gum health – Q2 (OR = 0.39), loose teeth – Q3 (OR = 63.0), brushing of teeth – Q4 (OR = 0.65), use of mouthwash – Q4 (OR = 0.69) and poor tooth appearance – Q5 (OR = 48.42). A recommended set of questions and proposed scoring system based on the logistic regression analysis of each predictors’ strength was then formulated. The use self-reported oral health questions appears to be a potentially useful screening tool for predicting the presence of serious periodontitis among type 2 diabetics locally where resources are limited and routine clinical oral examinations are not feasible. This will provide a cost-effective and rapid method of identifying patients who are in need of immediate dental evaluation and would benefit most to a dental referral.

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**EP412**
The effect of MCP-1 A-2518G polymorphism on development of diabetic coronary artery disease
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Introduction
Inflammatory markers play an important role in the development of type 2 diabetes and coronary artery disease. Monocyte chemoattractant protein-1 (MCP-1) is a member of the C-C chemokine family and a potent chemotactic factor for monocytes.

The aim of our study was to investigate the effect of MCP-1 A-2518G polymorphisms on the development of diabetic coronary heart disease.

Subjects and methods
53 diabetic patients with coronary heart disease, 64 diabetic patients without coronary heart disease and 61 healthy controls were genotyped. Diabetes was diagnosed according to the criteria of the American Diabetes Association (ADA) and the non-diabetic subjects were selected according to no past history of diabetes mellitus or impaired glucose tolerance. PCR-RFLP method was used for genotyping.

Results
There were significant differences between diabetic patient with coronary heart disease and control groups in MCP-1 A-2518G genotype (P: 0.01% 2: 9.11) and allele distribution (P: 0.01% 2: 6.53). MCP-1 AA genotype was significantly increased in coronary artery patients compared with controls but MCP-1 G allele frequency was increased in controls.

Conclusion
We found that MCP-1 2518 AA genotype may associate with diabetic coronary artery disease susceptibility while G allele seems to have protective effect against diabetic coronary disease.

Disclosure
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**EP413**
Phenotype-directed personalisation of therapy in type 2 diabetes mellitus patients and criteria of prescription
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Methods
We studied 228 patients with T2DM treated in Pauls Stradiņš Clinical University Hospital in Endocrinology Department from Jan 2013 to Sep 2014. The greatest attention was paid to the patients' biochemical analyses, such as triglycerides (TG), c-peptide, HbA1c and prescribed treatment, as well as BMI and the doctor who treated each patient. Phenotypically patients were divided into four major groups. The first group included 73 patients with chronic kidney disease (GFR < 60 ml/min per 1.73 m²), the second – 31 patient with obesity (BMI > 30 kg/m²), 66 persons represented older patients group (> 65 years old) and 58 – with early diabetes (< 10 years).

Results
For patients with obesity, treatment was started with insulin and metformin combination; chronic kidney disease group – with insulin monotherapy; in groups of old patients (> 65 years) and early diabetes patients – with insulin monotherapy. Insulin monotherapy was used for patients with c-peptide 0.1-0.9 ng/ml; for patients with c-peptide 1-2 ng/ml was used metformin combination with insulin, but patients with c-peptide more than 2 ng/ml were treated more often with DPP-4/metformin combination with insulin. There was no correlation between HbA1c level and prescribed therapy. For patients with TG level from 1.7 to 5.6 mmol/l was used metformin together with insulin, with TG < 1.7 mmol/l – only insulin, but with TG over 5.7 mmol/l DPP-4/metformin combination with insulin. We found some correlation between prescribed therapy and treating physicians: three of five physicians treated their patients more often with insulin. One treated patients mostly with combination of insulin and metformin, while last – with combination of DPP-4/metformin and insulin.

Conclusion
As T2DM is a special medical condition that requires an individualised approach to each patient to achieve adequate glycaemia and HbA1c levels.

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**EP414**
Glucogenic hepatopathy: a rare and underdiagnosed condition in type 1 diabetes
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Introduction
Glucogenic hepatopathy (GH) has been reported as a very rare and under recognized complication in longstanding poorly controlled type 1 diabetes patients. GH is characterised by transient elevation of liver transaminase and hepatomegaly caused by reversible and excessive glycogen accumulation in hepatocytes. Here we report a 20 years old type 1 poorly controlled diabetic female patient with elevated transaminases.

Clinical presentation
A 20-year-old type 1 diabetic female with poor glycaemic control, complicated by recurrent diabetic ketoacidosis (DKA) was admitted, with symptoms of fatigue, nausea, abdominal pain, and vomiting. Her glycemia had been poorly controlled with several episodes of DKA for several years. Her physical examination revealed hepatomegaly. Abdominal US showed mild fatty change of liver and mild hepatomegaly. Her HbA1c, 14.2%; SGOT: 79 (0–35) U/l; SGPT: 97 (0–55) U/l; ALP: 125 (47–119) U/l and GGT: 247 (4–24) U/l. Auto-antibody including anti-nuclear antibody (ANA), smooth muscle antibodies (ASMA), and mitochondrial antibodies (AMA) were all negative. Thyroid function test, serum copper, alfa antitriopin, and serum ceruloplasmin were also normal. The serologic findings for viral infection such as IgM anti-HAV, HBsAg, anti-HCV, HCV-RNA, cytomegalovirus, and Epstein-Barr virus were also all negative. Serum albumin and coagulation tests remained normal. She was not an alcohol or drug consumer and was not taking any medication except insulin. In addition, she did not show any symptom and sign compatible with acute hepatitis. So, we recommend her for a liver biopsy to elucidate the cause of acute elevation of liver enzyme. In hematoxylin and eosin stain, liver biopsy showed normal liver architecture, however, the hepatocytes were diffusely swollen with pale cytoplasm. The periodic acid-Schiff (PAS) staining showed abundant glycogen accumulation within hepatocytes. So, histologically, it was diagnosed as a glucogenic hepatopathy. Six weeks later, her transaminases were dropped to high normal levels via glycaemic control.

Conclusion
GH is a rare cause of increased transaminases in diabetic patients. Clinician awareness of GH should prevent diagnostic delay and will provide better insight into the prevalence of GH.

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**EP415**
Assessment of dependence of the hypoglycaemic episodes frequency on gender factor
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Objective
Assessment of the frequency of hypoglycaemic episodes during daily monitoring of glucose in the subcutaneous water of women and men with type 1 diabetes mellitus.

Methods
The study involved 162 patients with type 1 diabetes mellitus. The patients were divided into two groups: group 1 – women with regular menstrual cycle (n = 117) and group 2 – men (n = 45). The groups were compared in mean age (29.14 ± 7.56 years) and duration of type 1 diabetes mellitus (10.74 ± 7.67 years).

Results
In the first group of women 53%, registered hidden hypoglycaemic episodes, and 47% were not observed (P < 0.05). In the second group of men 69% has been registered hidden hypoglycaemic episodes, and 31% were not observed (P < 0.01). As for the incidence of hidden hypoglycaemic episodes between the groups, the significant differences were not observed (in the first group – 53% and in the second group – 69%), P > 0.05. Depending on the time of day, the incidence of hidden hypoglycaemic episodes (in the first group – 83% and in the second group – 75%) prevailed in comparison with explicit (in the first group – 17% and in the second group – 25%), P < 0.001. The daytime incidence of hypoglycaemic episodes in the first group was 72%, in the second group was 85% in comparison with the incidence of night hypoglycaemic episodes (in the first group – 28% and in the second group – 15%), P < 0.05.
Conclusions
i) Regardless of gender, the bulk of the cases occurred in hidden hyperglycaemic episodes compared with explicit ones. ii) The incidence of hidden day-time hyperglycaemic episodes was prevailed over the night incidence of hyperglycaemic episodes, regardless of gender. iii) The incidence of hidden hyperglycaemic episodes does not depend on gender.

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Comparison of umbilical cord ghrelin concentrations in full-term pregnant women with or without gestational diabetes
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Purpose
The purpose of this study was to analyse ghrelin concentrations in the umbilical cord of pregnant women with a diagnosis of gestational diabetes mellitus. The relationship between ghrelin concentrations and birth weights was investigated.

Materials and Methods
Sixty pregnant women with gestational diabetes mellitus and 64 healthy pregnant women without three oral glucose tolerance test results within normal limits were included in the study. Following birth but before extraction of the placenta, 10-ml blood samples were drawn from the umbilical vein in both groups. Ghrelin concentrations were measured.

Results
The mean birth weights of the babies born to mothers with GDM were higher than those in the control group (P = 0.04). The cord blood ghrelin levels in pregnant women with GDM were significantly lower than those of the healthy women in the control group (879.6 pg/ml vs 972.2 pg/ml; P = 0.03). The umbilical cord blood ghrelin concentrations in pregnant women with GDM undergoing insulin therapy were significantly lower than those of the control group (792.61 pg/dl vs 972.2 pg/dl; P = 0.01). Inverse correlations were detected between umbilical cord blood ghrelin levels and birth weights of the babies both in the group with GDM patients (r: −0.785; P = 0.001) and in the control group (r: −0.749; P = 0.001).

Conclusions
In pregnant women with GDM, umbilical cord ghrelin concentrations are closely related to the birth weights of the babies. Ghrelin presumably may be among the factors influencing foetal development potentially with its GH stimulating effects or by means of other mechanisms.

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Staphylococcus aureus nasal carriage and related risk factors in diabetic foot patients
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Introduction
Infections are the major cause of increased mortality and morbidity rate in diabetic foot patients. There are little data in literature about the effects of Staphylococcus aureus nasal carriage on DF infection, the risk factors that
influence nasal carriage and its incidence in diabetics. We aimed to detect of the incidence, risk factors and relationship between wound culture and *S. aureus* nasal carriage in diabetic patients who have DF with this study.

**Material and methods**

The study was designed as a prospective, cross-sectional, controlled study. Group 1 (*n* = 40): nondiabetic patients, group 2 (*n* = 40): diabetics without DF; and group 3 (*n* = 40): diabetics patients with DF. The incidence of *S. aureus* nasal carriage and effects of determined factors to nasal carriage were investigated in these three groups. The relationship between nasal carriage and wound culture was analysed in the last group.

**Results**

We found the incidence of *S. aureus* nasal carriage 17.5, 20, and 10% in the groups 1–3 respectively (*P* < 0.05). Determined parameters (age, sex, usage of insulin/oral anti-diabetic drugs, time of diabetes, level of Hba1C, and levels of fasting and after meal glucose) did not affect the *S. aureus* nasal carriage. We did not detect the relationship between wound cultures and nasal swap cultures in group 3. We observed no effect of the history of antibiotic usage in the last 6 months and existence of hospitalization or operation on *S. aureus* nasal carriage.

**Conclusion**

We detected that having diabetes and/or DF did not alter the risk of *S. aureus* nasal carriage and also carriage did not affect the results of wound culture. Better designed studies are needed for the detection of possible relationship between the factors belongs to the patients who have higher risk for *S. aureus* infections and nasal carriage.

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**EP420**

**The role of fetuin A as a biomarker of atherosclerosis and its relation to type 2 diabetes**

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**Background**

Hyperglycaemia produces various changes in the vascular tissue at the cellular level that accelerates the atherosclerosis. There is a direct correlation among carotid arterial stiffness and serum fetuin-A level. Fetuin-A is a marker of the inflammatory nutritional state and acts as a protective agent because it solubilises the calcium phosphate salt.

**Aim of this work**

To study the role of fetuin A in atherosclerosis and its association with type 2 diabetes.

**Subjects and methods**

This cross sectional study was conducted on 50 subjects aged from 40 to 60 years old divided into group I: 20 T2DM patients having atherosclerosis. Group II: 20 non diabetic patients having atherosclerosis. Group III: ten healthy subjects as control group. They were subjected to full clinical history, thorough clinical examination, laboratory investigations including fasting and 2-h postprandial blood glucose level, Hba1C, lipid profile, measurement of plasma fetuin-A level using ELISA, and measurement of carotid intimal thickness using duplex ultrasound.

**Results**

There was a highly significant difference between the three groups as regard SBP, DBP, FBG, PBG, Hba1C, TG, HDL-c, LDL-c, carotid intimal thickness, and fetuin-A level (*P* < 0.001) and on comparing the diabetics with atherosclerosis (group I) with non diabetics with atherosclerosis (group II) we found a highly statistical significant decrease in plasma fetuin-A level (*P* < 0.001) being lower in group (I) and a highly significant increase in carotid intimal thickness, SBP, and LDL-c (*P* < 0.001) in group I. We also found a highly significant negative correlation between fetuin-A and SBP, LDL-c, and carotid intimal thickness (*P* < 0.001). A significant positive correlation was also found between carotid intimal thickness and SBP, Hba1C, and LDL-c (*P* < 0.05). We found that the cut-off point of fetuin-A level using the ROC curve is 125 mg/ml with 100% sensitivity, 90% specificity, 97.1% accuracy, and a positive predictive value of 97.6%.

**Conclusion**

Our results postulate that there is an association between lower plasma fetuin-A level and the development of atherosclerosis especially in those having type 2 diabetes.

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**EP421**

**Association of plasma fetuin-A levels and peripheral vascular disease in type 2 diabetic patients**

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Ain Shams University, Cairo, Egypt.

**Background**

Diabetes is a risk factor for both PAD and PAD-associated mortality. Diabetic patients have worse arterial disease and a poorer outcome than nondiabetic patients. Fetuins are blood proteins made in the liver more abundant in fetal blood. Fetuin-A is regarded as an inhibitor of systemic calcification.

**Aim of this work**

To assess the relationship between plasma fetuin-A levels and peripheral vascular disease in type 2 diabetes mellitus.

**Subjects and methods**

This cross sectional study was conducted on 50 subjects aged from 50 to 65 years old divided into group 1: 20 T2DM patients with PVD. Group 2: 20 T2DM patients without PVD. Group 3: ten healthy subjects as control group. They were subjected to full clinical history, thorough clinical examination, laboratory investigations including fasting and 2-h postprandial blood glucose level, Hba1C, measurement of plasma fetuin-A level using ELISA and arterial Doppler ultrasound on peripheral vasculature for assessment of ankle peak systolic velocity (APSV).

**Results**

There was a highly significant increase in weight and BMI, FBG, and PBG in group 1 (diabetics with PVD) and group 2 (diabetics without PVD) than group 3 (control) (*P* < 0.001). While there was a highly significant decrease in plasma fetuin-A level and APSV in diabetics with PVD when compared with diabetics without PVD and also when compared with control (*P* < 0.001). While there was no statistical significant difference between group 2 (diabetics without PVD) and group 3 (control) as regard fetuin-A level (*P* = 0.065). There was a highly statistical significant decrease in plasma fetuin-A level and APSV (*P* < 0.001) being lower in group 1 than group 2 but there was no statistical significant difference as regard weight, height, BMI, FBG, PBG, and Hba1C. There was a highly significant positive correlation between fetuin-A and APSV (*r* = 0.737, *P* < 0.001) but a negative non-significant correlation between fetuin-A and the other parameters.

**Conclusion**

These results postulate an association between lower plasma fetuin-A level and peripheral vascular disease in type 2 diabetic patients.

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**EP422**

**Glycaemic variability in pregnant women with gestational diabetes**

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**Introduction**

The accurate and comprehensive assessment of glycaemic control in pregnant with gestational diabetes (GDM) is important for preventing foetal complications. We aimed to determine glycaemic variation on women with GDM with using a continuous glucose monitoring system (CGMS) and to investigate the relationship between reflecting glucose markers such as Hba1C, fructosamine (FRM), and 1,5-anhydroglucitol (1,5-AG).

**Materials and methods**

31 women with GDM on diet therapy only (mean age 31.9 ± 6.9 years, gestational week ≥35) were recruited from outpatient clinic. Those patients were screened by self-monitoring blood glucose (SMBG) and monitored for three consecutive days to obtain mean daily glucose data; glycaemic fluctuations were evaluated using postprandial incremental area under curve (AUC) and percent of mean absolute difference (MAD%). Venous blood samples were collected to measure Hba1C, FRM, and 1,5-AG.

**Results**

Prepregnancy BMI of participants was 26.2 ± 5.9 kg/m², weight gain during pregnancy was obtained as 12.2 ± 5.4 kg; levels of reflecting glucose markers were measured as following: Hba1C 5.0 ± 0.3 %, FRM 2.1 ± 0.2 μmol/l, and 1,5-AG 17.0 ± 4.9 mg/ml; according the results of CGM, MAD % was found as 6.7 ± 3.1%, the total number of fluctuations in glucose levels were counted as 5.8 ± 3.6. Glucose figures, measured by SMBG or CGMS were found similar (82.9 ± 10.2 and 86.1 ± 10.3 mg/dl); 1 statistically, there wasn’t any correlation between
determinants of CGM and other glucose reflection parameters. It was realised that birth of weight and size of head circumference of babies were affected by maternal glucose levels.

Conclusion
Although, it seems that normoglycaemia is sustained, there should be glucose variability in diabetic patients especially during pregnancy and all known glucose reflecting parameters do not show fluctuations. CGMS is an alternative method for detecting glucose variations in spite of having difficulties to afford and apply the tool. We concluded that higher glucose fluctuations were observed on pregnant with GDM who have high triglyceride at fasting and high glucose levels at third hour of OGTT at the beginning.

Disclosure
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EP423
Sexual function in women with diabetes at a Diabetes Care Unit
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The true prevalence of sexual dysfunction in women with diabetes is difficult to estimate. Studies of the area have shown varying and conflicting results. There is also disagreement about the conditions that influence this relationship and the risk factors that can be linked to the phenomenon. The purpose of this study was to investigate sexual function in women with diabetes at a Diabetes Care Unit. The study was conducted using a quantitative approach. Fifty women aged 18–65 years with type 1 or type 2 diabetes were enrolled in the study in which respondents were asked to complete a questionnaire containing background questions and the questionnaire, Female Sexual Function Index (FSFI). Twenty-nine women with diabetes who experience sexual dysfunction. The majority of the women felt that it was important to discuss changes in sexuality linked to diabetes. In addition, the majority stated that it was not informed about the area through their clinic.

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EP425
Obstructive sleep apnoea, incident type 2 diabetes mellitus, and cardiovascular risk
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Obstructive sleep apnoea (OSA) is a condition strongly associated with cardiovascular disease. Obesity is often related to both clinical problems and it is also a risk factor for incident type 2 diabetes mellitus (T2DM).

Aim
To assess cardiovascular risk among a cohort of patients with OSA in order to identify and optimise treatment of high risk patients.

Methods
Prospective study that included 72 patients with OSA under continuous positive airway pressure treatment. In all patients hypertension, T2DM, dyslipidaemia, smoking status, and history of cardiovascular disease were assessed; blood pressure (BP), body weight and height, waist circumference and neck size were measured; and BMI was calculated. Blood and urine samples were taken to evaluate fasting plasma glucose, cholesterol levels, glomerular filtration rate, microalbuminuria and HbA1c. T2DM was diagnosed with ADA criteria, and score was used to evaluate global cardiovascular risk and stratify high risk patients (score ≥5) in non diabetics.

Results
Of the 72 patients, 73% were male. Mean age was 52 years, and mean BMI 34.4 kg/m². At baseline, 52% had hypertension, 40% uncontrolled systolic BP, 50.8% dyslipidaemia, 15% T2DM, 39% impaired fasting glucose (IFG), 7.6% previously unknown DM, 8.9% microalbuminuria, 44% a score >5, and 38% were current smokers. There was a significant relationship between neck size (43.50 cm vs 40.52 cm, P < 0.05) and BMI (35.7 kg/m² vs 33.4 kg/m², P < 0.05) with IFG, and a significant association between apnoea–hypopnoea index (48.8 vs 37.3 apnoeas/h, P < 0.05) with high cardiovascular risk.

Conclusions
Compared with the general population, patients with OSA studied had a high cardiovascular risk and a high frequency of IFG and T2DM, especially in those with grade 2 obesity and a bigger neck size. Screening for diabetes and other cardiovascular risk factors in this population may be of particular interest.

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Simultaneous pancreas–kidney transplantation effect on stabilisation/progression of diabetic complications in patients with type 1 diabetes

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Objective
To evaluate the simultaneous pancreas–kidney transplantation (SPK) effect on stabilisation/progression of complications in patients with T1DM.

Materials and methods
The study included 16 patients after SPK. Eleven peoples received standard triple immunosuppressive therapy during the study period, five patients canceled steroid therapy after 6 months. The average age was 34 years old (31; 40), duration of T1DM 22 years (20.5; 28), the duration of diabetic nephropathy10 years (8; 14.5). The duration of dialysis therapy was 2 years (0.9; 2.5). All patients remained in the study for at least months 21 (10; 36) after the transplantation. Pancreas transplant chronic rejection with normal kidney transplant function was observed in one patient in 1 year after the operation.

Results
The mean level of Hba1c before the study was 8.65% (8.4; 9.1), then decreased to 5.6% (5.5; 5.8) after SPK. According to a continuous glucose monitoring system using «iPro2» euglycaemia (glycaemia (mmol/l) 3.9–8.9–89%, lower than 3.9–11%, and higher than 8.9–0%) was marked during the day. The level of C-peptide was 2.02 ng/ml (1.07–2.77), of insulin 12.5 µU/ml (11.4; 15.3), and GFR 76 ml/min per 1.73 m² (68; 90). All patients had normoalbuminuria, normal levels of hemoglobin 120 g/l (112; 130), parathormone 77.3 pg/ml (60.4; 92.5), phosphorus 1.2 mmol/l (1.05; 1.4), and blood pressure 110 mmHg (100.0; 120). The proliferative diabetic retinopathy progression which required vitrectomy and additional laser panretinal photocoagulation was observed in 17.5% of patients. Nonstenotic atherosclerosis of the lower extremities was detected in 13 peoples, ulcerative defects in the lower limbs in five patients and chronic osteoarthropathy progression in four cases.

Conclusions
Despite the euglycaemia and renal function normalisation after SPK the progression of diabetic complications was observed. This fact indicates the need of further monitoring and treatment in this category of patients.

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Lixisenatide clinical experience on patients with type 2 diabetes and obesity in Endocrinology Offices

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Introduction
Some treatments of diabetes, such as lixisenatide, improve global metabolic status beyond glycaemic control.

Aim
To evaluate tolerance to lixisenatide and its effects on weight and 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 lixisenatide treatment.

Results
We studied 104 patients (51% women) with type 2 diabetes and obesity. Average age was 58.4 ± 10.5 years, average duration of diabetes was 11.2 ± 6.7 years, and 35.6 and 69.6% had family history of cardiovascular disease and diabetes respectively. At baseline, 92.2% of the patients had oral hypoglycaemic agents, 13.5% GLP1 agonists and 67.3% insulin (44.2% basal insulin, 12.5% premixed insulin, and 10.6% basal-bolus insulin). We re-evaluated the patients 3.8 ± 1.6 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 = 0.022), total-chol (P < 0.001), LDL-chol (P = 0.046), TG (P = 0.020), hypertension drugs (P < 0.001), and lipid drugs (P < 0.001). We checked that blood pressure and lipid improvement were not due to hypertension and lipid treatment intensification. No changes in levels of amylase related to lixisenatide treatment were observed. Regarding digestive tolerance to lixisenatide, 7.9% of patients did not tolerate, 5% tolerated 10 µg/day, and 85.1% tolerated 20 µg/day.

Conclusions
Significant improvement of anthropometric parameters and glycaemic control in terms of fasting glucose and HbA1c, and significant decrease of blood pressure and total cholesterol were observed. Lixisenatide was safety and well tolerated in most patients. In addition, we found a significant intensification of antihypertensive and lipid-lowering therapy, not only glycaemic control, in our clinical practice with an overall metabolic approach of patients.

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Nonglycemic effects of incretins in patients with long history diabetes type 1 and chronic kidney disease

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Aims
To estimate the nonglycemic effects of incretins in patients with long history of type 1 diabetes (T1D) and chronic kidney disease (CKD).

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Materials and methods
We examined 75 patients with a long history T1D (more than 20 years) and CKD on the different stages: 32 patients with CKD at the stages 1–4, 17 patients on hemodialysis, 11 with kidney transplantation, and 15 patients without CKD. In addition to routine methods of investigation we have estimated mineral and bone disorders (MBD) factors (phosphorus (P), phosphorous and calcium product (PxCa) parathormone (PTH), 25(OH)vitamin D (vitamin D), and fibroblast growth factor 23 (FGF 23)), determined a multiphasic computed tomography of heart with Agatston index definition. Markers of proinflammatory (monocyte chemoattractant protein-1 (MCP-1) and C-reactive protein (CRP)), fibrosis (transforming growth factor-beta (TGFβ)), and cardiovascular collapse (atrial natriuretic peptide (NTPro-BNP)) were defined. Determining the level of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).

Results
The study showed no difference on the level of GLP-1 and GIP in patients with a long history of T1D, regardless of the presence and stage of CKD and the degree of compensation of diabetes. Received confirmation inverse relationship between GLP-1 and the level of total cholesterol (r = −0.320; P < 0.05), Agatston index (r = −0.317; P < 0.05), as well as the GYP and fibrinogen level (r = −0.285; P < 0.05), CRP (r = −0.626; P < 0.05), FGF-23 (r = −0.341; P < 0.05), and MCP-1 (r = 0.277; P < 0.05).

Conclusions
In patients with T1D is defined inhibitory role of incretins in the progression of atherosclerotic and MBD, actively involved in the development of cardiovascular disease, irrespective of the stage of CKD. The obtained data require further study from the standpoint of application nonglycemic effects of drugs of incretins in the treatment of patients with T1D.

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EP430
COMMODITY12 telemedicine system is effective in primary care setting in patients with type 2 diabetes
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Background
The COMMODITY12 is a telemedicine system designed for continuous monitoring of diabetes type 1 (DM1) and DM2, as well as the cardiovascular comorbidities. The system has been created in collaboration of nine European academic and industrial partners under FP7 (www.commodity12.eu).

Aim
The aim of this study was to assess clinical utility of the COMMODITY12 system in DM2 patients, under a design of a mini feasibility trial.

Methods
Sixty outpatients from Lodz region (central Poland) with DM2 were randomly ascribed to either control arm (n = 30), in which they received standard care, or intervention arm (n = 30), in which they used COMMODITY12 system for daily monitoring of their diabetes-related parameters (glucose level, blood pressure, weight, ECG, heart rate, mobility, a range of lab tests, and adherence to medication). All patients were monitored for a period of 6 weeks. Primary outcome measures was system operability and whole trial feasibility, defined as harmonic technical functioning of all layers of the system, and appropriateness of the personal health system (PHS) for patient use, respectively.

Results
In general, the COMMODITY12 system functioned well, with only some problems with transmission of the data from ECG sensor to the hub. Patients accepted telemedicine system well, and found it to be helpful in self-management of diabetes. System was effective in collecting and analysing data related to both diabetes, and comorbidities (such as hypertension, arrhythmias, or sleep apnoea). In some patients using COMMODITY12 system, trend toward better metabolic control was also observed, as compared to their previous results, as well as to the control group.

Conclusion
These results point at the usefulness of COMMODITY12 system in diabetes care. Further studies on larger groups are warranted to determine the effect of the system on clinical outcomes, as well as its cost-effectiveness.

Disclosure
This Study was a part of the Commodity12 Project (C0ntinuous Multi-parametric and Multi-layered analysis Of Diabetes T1ype 1 and 2, www.commodity12.eu), EU 7th framework programme.

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EP431
Microangiopathic complications in latent autoimmune diabetes in adults: relationship with thyroid autoimmunity
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Background
Patients with latent autoimmune diabetes in adults (LADA) are a clinically, immunologically, genetically heterogeneous group and the presence of thyroid autoimmunity (TA) appears to contribute to his heterogeneity.

The aim was to evaluate the impact of TA on microangiopathic complications in LADA patients.

Materials and method
LADA has been defined by the onset of diabetes at ages above 30 years, the lack of need for insulin therapy for at least 6 months after its first appearance, the presence of anti-GAD antibodies (GADA). Positive titers of anti-thyroid peroxidase antibodies (TPOAbs) were observed in 30 (28.8%) out of 104 LADA patients. Prevalence of retinopathy (DR), peripheral neuropathy (PN), autonomic neuropathy (AN), and diabetic nephropathy (DN) were also evaluated.

Results
Patients with TA had twice the risk of RD compared to patients without TA, odds ratios 2.27 (95% CI 0.8–5.7, P = 0.004). The risk of NP was 1.8 times higher in patients with TA compared with patients without TA (95% CI 0.7–4.4, P = 0.04). Patients with TA are three times more likely to develop AN than patients without TA, odds ratio 3.4 (95% CI 1.1–11, P = 0.014). From ten patients with DN, four of them (40%) had TA compared to 26 patients (27.7%) of 94 without DN. Patients with TA had the probability to develop this complication 1.7 times higher than those without TA, odds ratio 1.74 (95% CI 0.4–6.6, P = 0.46).

Conclusions
Except diabetic nephropathy, the presence of TA in patients with LADA has determined a significantly higher prevalence of microangiopathic complications.

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EP432
Evaluation series on safety and efficacy of nutritional supplements (ESENS) in newly diagnosed hyperglycaemia
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Diabetes is endemic in society. Beyond lifestyle modification (often short lived) and metformin, which while effective has gastrointestinal side effects, other available pharmacological options are challenging to implement across populations of newly diagnosed patients. The recent position statement by ADA/EASD calls for patient-centred individualised therapies to suit patients’ need. Glucose-lowering nutritional supplements may be an effective and safe option for newly diagnosed hyperglycaemia. But, their safety and efficacy have not been systematically evaluated in randomized clinical trials. In this 12-week, investigator-initiated, six-centre, randomized, double-blind, placebo-controlled, phase 3 trial, newly diagnosed subjects (n = 232) with FPG >100 mg/dl received PreCrea (a proprietary nutritional supplement containing standardized plant extracts and dietary elements) or placebo one capsule twice daily along with lifestyle modification. Primary endpoint was the change from baseline HbA1c at week 12. Secondary endpoint was change from baseline in FPG. At week 12, HbA1c was significantly reduced from baseline with PreCrea compared to placebo (−0.91 vs +0.08%; P < 0.001). Reductions in FPG in the PreCrea group compared to placebo (P < 0.028) (−23.1 mg/dl vs −7.2 mg/dl at week 12), with no hypoglycaemia, no weight gain and no adverse effects and no difference in safety parameters. PreCrea provided clinically important and statistically significant improvements in glycemic control compared to placebo. The efficacy (nearly 1% reduction in HbA1c), safety and tolerability profile of PreCrea
Intima–media thickness of internal carotid arteries in the diagnosis of coronary atherosclerosis in patients with type 2 diabetes and silent ischaemia

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Aims
To determine the role of intima–media thickness (IMT) of internal carotid artery (ICA) in the diagnosis of coronary atherosclerosis in patients with type 2 diabetes (T2D) and silent ischaemia (SI).

Methods
We provide a retrospective analysis of 60 cases of patients with T2D (24 men, age 60.5 ± 4.7 years), history of diabetes – 4.7 ± 0.5 years. SI was diagnosed by comparing complaints, anamnesis, ECG data and daily ECG monitoring. All patients underwent carotid ultrasound in B-mode to determine the degree of ICA IMT stenosis. The degree of coronary atherosclerosis was evaluated by coronary angiography (CAG).

Results
In 55% of patients with T2D and SI the presence of atherosclerotic lesions of two or three coronary arteries (CA) located in the middle and distal segments was identified. In 13% of patients with T2D critical stenosis of CA was found. ICA IMT values were significantly higher in patients with SI and coronary atherosclerosis compared to patients with T2D without atherosclerotic CA lesions (1.41 ± 0.12 vs 1.21 ± 0.11, P < 0.05), in 20% of patients with T2D and SI the presence of atherosclerotic plaques of ICA was revealed. When conducting multiple logistic regressions in patients with T2D and SI the following predictors of atherosclerotic CA lesions were identified: duration of T2D (OR 4.07, 95% CI 2.56–6.42; P < 0.05), dyslipidaemia (OR 2.17 95% CI 1.47–3.12; P < 0.05), gender (OR 1.52, 95% CI 1.14–2.31; P < 0.05), and ICA IMT (OR 2.81, 95% CI 1.76–3.21; P < 0.05). AUC value in the analysis of ROC-curve for ICA IMT was 0.75 (95% CI 0.61–0.79; P < 0.05).

Conclusion
Increased thickness of ICA intima–media and CA atherosclerotic plaques combined with coronary atherosclerosis in patients with T2D and SI should be considered during the screening of this group of patients to identify those to perform CAG and early revascularisation for the prevention of cardiovascular events.

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**EP436**

**Stroke in prediabetic patients**

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**Objective**

To describe the clinical characteristics of stroke in patients with prediabetes (pre-DM) and to compare them with DM and non-DM patient characteristics.

**Methods**

Retrospective analysis of a prospective series of acute stroke patients. Demographic and clinical characteristics were compared among the three groups, along with outcome data. Stroke severity was evaluated by modified Rankin scale (mRS) and NIHSS (NIH stroke scale).

**Results**

138 patients (50 non-DM, 32 pre-DM (23%), and 56 DM). Median age was 74.5 ± 15.35, 73.38 ± 15.20, and 73.84 ± 11.44 years respectively. 44% of non-DM, 53.1% of pre-DM and 58.9% of DM patients were men. The prevalence of other vascular risk factors in non-DM, pre-DM, and DM patients was:

- Hypertension (46, 71, and 89%)
- Hypercholesterolemia (42, 65, and 69%)
- Peripheral artery disease (4, 6.2, and 7.1%)
- Atrial fibrillation (6, 15.6, and 16%) Smoking habit was more common in pre-DM patients (13.5% vs 14% in non-DM patients and 7.5% in DM patients).

**Conclusion**

Stroke characteristics: prevalence of ischemic stroke (IS) was 88% in non-DM patients, 84.3% in pre-DM and 94.6% in DM patients (P = 0.24). Transient ischemic attack was more common in non-DM patients (36.3% of IS vs 33.3% in pre-DM and 20.7% in DM patients) (P = 0.28). There were no differences in stroke severity between non-DM, pre-DM, and DM patients (4.9 ± 6.2, 4.5 ± 6.7, and 4.9 ± 5.4 NIHSS median points each group), neither in 3-month mortality (12, 12.5, and 7.1%) and in 3-month mRS (2.18 ± 2.12, 1.81 ± 2.21, and 1.96 ± 1.02). rtPA success rate was 80, 66, and 56.9% respectively (P = 0.91). P (all groups), *P (non-DM/pre-DM patients), and **P (pre-DM/DM patients).

**Discussion**

Frequency of pre-DM in higher than observed in general population (10%). Pre-DM patients occupy an intermediate situation regarding vascular risk factors but has no impact on stroke outcomes.

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**EP437**

**Diabetes mellitus as a conformational disease: a novel potential therapeutic approach**

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**Introduction**

Type 2 diabetes mellitus is a conformational disease (CD), characterised by deposition (fibrils and cytotoxic oligomers) of the human islet amyloid peptide (hIAPP). CDs have devastating effects on the sufferers and their caregivers, as well as a tremendous economic impact on families and the health system. Novel molecule candidates targeting self-assembled amyloidogenic proteins represent a potential therapeutic approach for CDs.

**Methods/design**

In this work we carried out a systematic study in order to determine the interrelation between the IAPP and IAPP 29–29 fragments in aggregation kinetic with a novel family of naphthalene compounds, used as chemical chaperones. N-(2-aminoethyl)-N'-1-naphthylsuccinamide A; methyl (2-4(1-naphthylamino)-4-oxobutanyl)amino)ethyl dithiocarbamate B; (2R)-2-(6-methoxy-2-naphthyl)propanoic acid (Naproxen) C; N-(4-(1-naphthylamino)-4-oxobutanyl)β-alanine D; 6-[(4-(1-naphthylamino)-4-oxobutanyl)amino] hexanoic acid E; N3,N3'-ethane-1,2-diybis(N1-1-naphthylsuccinimide) F; N-(4-amino-butyl)-N'-1-naphthylsuccinamide G; and (1E,6E)-1,8-bis(4-hydroxy-3-methoxysphenyl)octa-1,6-diene-3,5-dione (Curcumin). We describe the structural features, aggregation kinetics, and toxic properties of the, in presence or absence of a novel naphthalene of the chemical chaperones family.

**Results**

We found a stronger inhibitory effect in the fibril formation of the chaperones B, C, D, E, and G. Transmission electron microscopy showed the presence of long and curly fibers in the sample control, while the samples treated with chaperones A, B, C, D, and E generated several amorphous and disaggregated structures. A cytotoxic effect of the chaperones family on cerebellar granule cells was found in the MTT assays. Furthermore, the binding sites of the chemical chaperones to hIAPP were located by means of docking on the IAPP 3D model.

**Conclusion**

In this study we managed to obtain chaperones that bind to the native state, to the cytotoxic oligomers and the amyloid fibrils. Chaperones derived from naphthalene can regulate fibre formation processes by binding to the native state, minimising the formation of amorphous aggregates, as well as cytotoxic oligomers.

**Disclosure**

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**EP438**

**Continuous glucose monitoring systems and the improvement in hypoglycaemic awareness post-islet transplantation: a single-centre cohort study**

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**Background**

Islet transplantation is an NHS-funded procedure introduced to the UK in 2011 for patients with the most severe type 1 diabetes mellitus (T1DM). These particular patients have unstable blood glucose, frequently occurring episodes of severe hypoglycaemia and impaired awareness of hypoglycaemia (IAH).

**Objectives**

To evaluate the effectiveness of islet transplantation in improving glycaemic control, reducing the burden of hypoglycaemia and improving awareness of hypoglycaemia through a single-centre cohort study at the Royal Infirmary of Edinburgh.

**Methods**

A retrospective analysis of data collected over 3 years from the 16 patients who have undergone islet transplantation in Scotland. HBAlc was measured and continuous glucose monitoring systems (CGMS) were utilised to assess glycaemic control, while Gold and Clarke score questionnaires tested IAH.

**Results**

Glycaemic control significantly improved, as illustrated by percentage time in hypoglycaemia in the months following transplant (P = 0.0211) and HBAlc (P = 0.0426). Improved Clarke (P = 0.0034) and Gold (P = 0.0001) scores indicate improved glycaemic awareness following transplant.

**Conclusion**

Our observations in 16 patients suggest that in selected patients, islet transplantation can be a life-changing procedure capable of improving glycaemic control and IAH in select patients with a history of frequent and severe hypoglycaemia. Data can be collated with that from other UK centres to increase statistical power and establish statistical significance for correlation statistics.

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**EP439**

**HDL levels is associated with left ventricular ejection fraction in type 2 diabetic patients**

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**Introduction**

Considering the high prevalence and significant morbidity and mortality of heart failure in type 2 diabetic patients, identification of risk factors for cardiac...
dysfunction is important. The ejection fraction represents how well the heart is pumping out blood and is used to diagnose heart failure. In this study, we investigated the factors associated with left ventricular ejection fraction (LVEF) in type 2 diabetic patients.

Methods
A total of 369 type 2 diabetes patients were included in the present study. We conducted trans-thoracic Doppler echocardiography for evaluating cardiac function. Height, body weight, blood pressure, and biochemical markers were measured for each patient.

Result
The mean age of total patients was 61.24 ± 12.27. The mean LVEF was 58.63 ± 9.15%. In total patients, HDL was significantly positively correlated with LVEF (r = 0.163, P = 0.002). This significant association was retained in multivariate analysis adjusted for age, BMI, creatinine, haemoglobin, and presence of hypertension (r = 0.164, P = 0.003). In order to rule out the possibility of increasing LVEF due to diastolic heart failure, we performed subgroup analysis. In patients with type 2 diabetes who have normal diastolic function, LVEF and HDL was significantly positively correlated (r = 0.246, P = 0.013). Triglyceride (TG) was significantly negatively associated (r = -0.217, P = 0.029). After adjusted by age, BMI, creatinine, haemoglobin, and presence of hypertension, the positive correlation between LVEF and HDL was retained (r = 0.206, P = 0.045). TG was not associated with LVEF after adjustment (r = -0.089, P = 0.393).

Conclusion
In the present study, we found that HDL level is significantly associated with LVEF in type 2 diabetic patients with or without diastolic heart failure. This suggests that the treatment for raising HDL might have a role in the improvement of heart function in type 2 diabetic patients.

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**EP441**

**Glargine insulin treatment during pregnancy in type 1 diabetes mellitus**

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Objective
The aim of this study was to evaluate maternal and neonatal outcomes in women with type 1 diabetes mellitus (DM1), and analysing differences associated to insulin glargine exposure during pregnancy.

Patients and methods
Retrospective descriptive study of pregnancies in women with DM1 (2004–2012). Variables analysed: baseline characteristics (age, time of diabetes evolution, microvascular complications, and weight), maternal outcomes (weight gain, HbA1c, hypoglycaemia, preeclampsia, abortions, and vaginal delivery and caesarean section) and neonatal outcomes (gestational age at delivery, birth weight, and congenital malformations). The pregnancies were divided in groups attending to their exposition to glargine insulin and were analysed to evaluate possible differences between them (group 1: exposed and group 2: unexposed).

Statistical analysis
Comparing proportions with the χ² and comparing means with Student’s t-test.

Results
132 pregnancies in women with DM1. Group 1: 57 (43.2%) and group 2: 75 (56.8%). Baseline characteristics were similar in both groups. HbA1c was different before pregnancy (group 1 vs group 2: 7.95% vs 7.02%; P = 0.001), but similar during pregnancy (group 1 vs group 2: first trimester 6.83% vs 6.47%; second trimester 6.45% vs 6.33%; and third trimester 6.67% vs 6.42%; P > 0.05). Maternal weight gain was similar in both groups (group 1 vs group 2: 10.28 kg vs 11.02 kg, P = 0.4). Maternal and neonatal outcomes (group 1 vs group 2): abortions 1 (2%) vs 9 (12%), P = 0.05; caesarean section 18 (31.5%) vs 39 (52%), P = 0.005; gestational age at delivery 38.02 weeks vs 38.12 weeks, P = 0.93; macrosomia 13 (23%) vs 21 (28%), P = 0.29; congenital malformations 3 (23%) vs 6 (28%), P = 0.49; and neonatal hypoglycaemia 1 (2%) vs 5 (7%), P = 0.13.

Conclusions
The number of caesarean sections was higher in women not exposed to insulin glargine. Insulin glargine use before and during pregnancy is not associated with worse maternal and neonatal outcome, or congenital malformation.

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**EP442**

**Hemorheological alterations in type 2 diabetes patients with nephropathy**

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Background
Hemorheologic alterations or changes in blood viscosity have been suggested to play a role in the pathogenesis of diabetic microvascular complications. We measured various hemorheologic parameters in type 2 diabetes patients at different stages of chronic kidney disease (CKD) and assessed their possible role as early markers of diabetic nephropathy and renal insufficiency.

Methods
One hundred and five patients with type 2 diabetes were divided into four groups according to glomerular filtration rate (GFR). Hemorheologic parameters, including erythrocyte deformability, fibrinogen/elongation index (EI), and aggregation index (AI) were measured using microfluidic hemorheometer. Various metabolic parameters were assessed from fasting blood samples and urine albumin/creatinine ratio (ACR) was calculated from first morning voided urine.

Results
There were significant differences in RBC deformability, AI, critical stress, fibrinogen/EI, and albumin/creatinine ratio among patients in different stages of CKD (all P < 0.05). RBC deformability and fibrinogen/EI significantly differed between normal and CKD 2 patients while there was no such difference in ACR. In multiple regression analysis, fibrinogen/EI at 3 Pa was an independent predictor of GFR (β = −0.328, P < 0.05). Also, AI, critical stress, and fibrinogen/EI were significantly different among patients at different stages of diabetic nephropathy, with a significant difference in fibrinogen/EI between normal and microalbuminuric patients (all P < 0.05).

Conclusions
RBC deformability and fibrinogen/EI are sensitive parameters measured via point-of-care testing for detecting erythrocyte alterations in early CKD and...
nepathic pain. Further studies are warranted to verify their use as screening tools for diabetic neuropathic and renal impairment.

Disclosure
This study was supported by a grant of the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (HI12C0122, 2012).

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EP443
Impact on quality of life in peoples with painful diabetic peripheral neuropathy
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Objective
This study was performed to determine the impact on quality of life and sleep impairment of diabetic peripheral neuropathy (PDPN).

Research design and method
The study pool consisted of 200 randomly selected peoples with type 2 diabetic peripheral neuropathy. PDPN was diagnosed using visual analogue scales (VAS) and medical history. The patients were asked to answer the Brief Pain Inventory-Short Form (BPI-SF), Medical Outcomes Study Sleep (MOS-Sleep) Scale, EuroQol (EQ-5D), and VAS and estimate the quality of life in people with diabetic peripheral neuropathy.

Results
Among the patients with diabetic peripheral neuropathy (n=200), 82 (41%) were diagnosed with PDPN. PDPN was independently associated with age, fasting plasma glucose, hypertension, dyslipidemia, and previous cerebrovascular events. All pain severity and interference measures were higher in patients with PDPN than those in patients with painless DPN and patients with PDNP reported more impaired sleep and lower EQ-5D and VAS scores. 200 patients had DPN and Pain Severity Index and pain interference items such as general activity, mood, walking, normal work, relationship, sleep, and enjoyment of life in BPI-DPN were higher in patients with painful DPN compared to those in patients with painless DPN. MOS-6 items-sleep adequacy, respiratory problem during sleep, sleep initiation problem, sleep maintenance problem, and somnolence-sleep scale were lower in patient with painful DPN than painless DPN. EQ-5D index were lower in patients with painful DPN compared to those in patients with painless DPN.

Conclusions
Patients with painful DPN have greater discomfort during daily activities and sleep, and reduced QoL compared to patients with painless DPN. This study provides an extent of the impact of pain on QoL in patients with painful DPN and physicians should carefully consider pain symptoms in patients with diabetic peripheral neuropathy.

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EP444
Prevalence and management of peripheral diabetic neuropathic pain in a hospital diabetes clinic: how are we doing?
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Introduction
Peripheral diabetic neuropathic pain (PDNP) as a significant complication of diabetes mellitus (DM), which is present in 16–26% of patients. NICE UK guidelines recommend that physicians should make a formal enquiry about distressing neuropathic symptoms annually and that either duloxetine, amitriptyline, gabapentin, or pregabalin should be used as first-line treatment for distressing neuropathic symptoms annually and that either duloxetine, amitriptyline, gabapentin, or pregabalin should be used as first-line treatment for distressing neuropathic symptoms annually.

Aims
To assess the prevalence PDNP in a diabetic cohort and whether management was according to NICE guidelines. Patients attending an outpatient clinic in SWBH, Birmingham were prospectively consented to answer questions regarding sensations in their feet and lower legs using an adapted and validated questionnaire from the ‘Lily Toolkit’ and validated ‘S-LANSS score’ for identifying pain of neuropathic origin.

Results
A total of 100 patients (July–Oct 2014) agreed to answer questions, of which 65% were males (average age 62 years). 98% of patients had an annual foot check: via GP (88), podiatrist (6), or hospital specialist (4), with formal assessment of their ulcer risk but did not include questions about painful neuropathy. 27% (n=27) patients admitted getting pain in their feet or lower legs, which was consistent with PDNP. The average pain score in this group was seven out of ten and two-thirds had spoken to a healthcare professional about their symptoms in the past. Of these, 5/27 (19%) were on one of the recommended medications for PDNP; amitriptyline (n=1), gabapentin (n=2), and combined amitriptyline and gabapentin (n=2).

Discussion
In this diabetic cohort, foot checks with respect to ulcer risk were reliably undertaken by the GP. However, 27% of patients had symptoms consistent with PDNP but nearly 79% weren’t on any of the first line treatments recommended by NICE. Would incorporation of questions about symptoms of PDNP into the annual primary care foot checks improve the detection rates and subsequently the management of these patients?

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EP445
The effect of metformin on spontaneous apoptosis in patients with type 2 diabetes
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Today, there are 382 million people living with diabetes. The overwhelming majority have a type 2 diabetes. Metformin is first-line drug for many of them.

Materials and methods
The study involved 26 patients in mean age 54.46±1.2 years (from 41 to 65), among them, 14 women and 12 men. 21 patients with newly diagnosed diabetes and five patients receiving treatment with sulphonylureas. All patients were prescribed metformin in mean dose 2000 mg. During the study were determined the levels of HbA1c and spontaneous apoptosis before and after treatment. Measurement of apoptosis were performed by flow cytometry.

Results

<table>
<thead>
<tr>
<th></th>
<th>Before treatment (n=26)</th>
<th>After treatment (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>8.34±0.24</td>
<td>7.57±0.22*</td>
</tr>
<tr>
<td>Spontaneous apoptosis (%)</td>
<td>15.9±1.7</td>
<td>11.8±1.2*</td>
</tr>
</tbody>
</table>

Significant difference between the indices before and after treatment (*P<0.05).

Conclusions
Metformin in the treatment of diabetes mellitus leads to a decrease in blood glucose and compensation of diabetes. And also metformin reduces the level of spontaneous apoptosis. However, studies of mitochondrial changes membrane potential revealed statistically (P<0.05) significant reduction cells with signs of apoptosis 15.9±1.7%–11.8±1.2% after 90 days of therapy. It the increase in mitochondrial activity and resistance MCs that turn points to restore energy components of blood cells. And no changes on indicators of surface markers indicating exactly on stimulatory effect of therapy.

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**EP446**
Microalbuminuria by concentration serum and urine levels of adropin in patients with type 2 diabetes mellitus
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**Abstract**
Microalbuminuria is an important public health problem due to defects of the effect of the insulin or insulin deficiency, accompanied by chronic microvascular complications with diabetic nephropathy is characterised by proteinuria that the increasing number of patients progresses to end stage renal disease. Many peptide hormone made in etiopathogenesis is situated, although adropin which discovered in recent years involves in glucose homeostasis, its relation to diabetes and nephropathy has still not been investigated.

**Methods**
The serum and urine levels of adropin in 20 healthy individuals to form a control group with total of 60 diabetic patients including normalalbuminuric 20, microalbuminuric 20, and overt albuminuric 20 ones were measured.

**Results**
Serum adropin levels compared with the overt albuminuric group were significantly as lower in healthy control, normalalbuminuric, and microalbuminuric groups (respectively; \( P=0.007, P<0.001 \), and \( P=0.008 \)). Adropin were found to be positively correlated with serum creatinine and microalbuminuria levels (respectively; \( P=0.031, r=0.242 \) vs \( P=0.001, r=0.379 \)). Adropin urine levels were significantly as higher in diabetic patients than in healthy control (\( P=0.001 \)). Compared with the normo and overt albuminuric groups, adropin urine levels were lower in microalbuminuric group (\( P=0.026 \) for both).

**Discussion**
As a result, the serum adropin levels appear to be increased in overt albuminuric group. The cause of increased activity of these peptides associated with endothelial function and energy homeostasis can be considered for renal hemostasis. Urinary adropin levels to be lower only in the diabetic microalbuminuric group. The study was aimed to investigate the possible direct aetiological link between adropin and diabetics mellitus with diabetic nephropathy were aimed to investigate.

**Conclusions**
Serum adropin levels appear to be increased in overt albuminuric group and may be considered as a potential factor in the initiation phase of diabetic nephropathy.

**EP447**
Remitting seronegative symmetrical synovitis with pitting oedema syndrome in association with saxagliptine: case report
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**Abstract**
Remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) syndrome is a very rare clinical entity including a tenosynovitis of the hands and wrists, and marked pitting oedema on upper and lower extremities. RS3PE has been suggested to be associated with many disease conditions and drugs. Saxagliptine is DPP4 inhibitor that relatively new oral hypoglycemic agent. This case is the second report of the occurrence of RS3PE in patients receiving a DPP4 inhibitor.

**Case**
A 51-year-old man presented with bilateral hand oedema. The symptoms onset within after initiating saxagliptine of the treatment. He had type 2 diabetes mellitus (HbA1c = 6.6%), and hyperlipidaemia. At the time of presentation, his other medications were metformin, premixed insulin (aspart and protamine), and rosvastatine. He did not have any history of drug allergy or systemic rheumatic illness. Physical examination revealed tenosynovitis characterized by swelling and moderate tenderness of the metacarpophalangeal and proximal interphalangeal joints bilaterally. There was marked non-tender pitting edema on the dorsum of both hands and wrist joints. Physical exam results were otherwise normal. Laboratory evaluation revealed normal ESR, and negative ANA, ANCA, RF, and ACPA. X-rays and MRI revealed only soft-tissue swelling without evidence of joint destruction. Owing to the absence of complete remission with removal of saxagliptine during the 4 weeks, saxagliptine was thought to be responsible for the aetiology of RS3PE syndrome. Than patient was treated with prednisone 20 mg daily. Clinical findings were dramatic response to prednisone.

**Conclusions**
This case demonstrates a possible direct aetiological link between saxagliptine and RS3PE.

**EP449**
Effects of dietary nitrate on metabolic status and myocardial ischaemia–reperfusion injury in type 2 diabetic rats
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**Abstract**
Considering the protective effects nitrate has against diabetes and cardiovascular diseases, we aimed to determine effects of dietary nitrate on metabolic status and myocardial ischemia–reperfusion (IR) injury in type 2 diabetic rats.

**Methods**
Rats were divided into four groups (\( n=7 \)): control, control + nitrate, diabetes, and diabetes + nitrate. Diabetes was induced by nicotinamide + streptozotocin, and nitrate added to drinking water (100 mg/l) of animals for 2 months. Serum nitrite+nitrate (NOx), glucose, lipid profile, total antioxidant capacity (TAC), catalase (CAT) activity, and systolic blood pressure (SBP) were measured before and after the study. After 2 months, i.v. glucose tolerance test was performed and hearts were perfused by Langendorff apparatus; before and after IR, LVDP, and dp/dt\(_{\text{max}}\), and heart levels of malondialdehyde (MDA) and NOx were measured.

**Results**
Diabetic rats had lower serum NOx values compared to baseline (29.2 ± 5.6 μmol/l vs 39.0 ± 3.2 μmol/l, \( P<0.05 \)), which normalized after nitrate therapy. Serum glucose in the diabetes + nitrate group was less increased, than the diabetes one (24.1% vs 90.2%; \( P<0.05 \)). Nitrate therapy in diabetic rats significantly improved glucose tolerance and decreased serum cholesterol, LDL-C, and triglycerides by 22.9, 54.2, and 47.6% respectively and increased serum HDL-C by 42.4% compared to baseline. Diabetic rats had lower TAC and CAT activity, which normalized after dietary nitrate therapy. Recovery of LVDP and \( + \text{dp/dt} \) were 15 and 17% lower in diabetic rats vs controls respectively, but almost normalized after dietary nitrate, which also restored elevated SBP to near normal status (131.2 ± 4.4 vs 120.6 ± 2.2). Compared to controls, heart NOx level was lower in diabetic rats before IR, but was higher after. Diabetic rats had higher MDA levels both before and after IR, which along with heart NOx levels stabilized following dietary nitrate.

**Conclusions**
Nitrate therapy improved glucose tolerance, restored dyslipidaemia, prevented increase in SBP, and provided cardioprotection against IR injury in diabetic rats.

**Disclosure**
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**Endocrine Abstracts** (2015) **Vol 37**
The influence of erythropoietin therapy on serum level of tumour necrosis factor alpha in anaemic patients with early stages of diabetic nephropathy
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Aims
Anaemia occurs early and predicts high risk of cardiovascular events and death in patients with diabetic nephropathy. In our previous studies we have shown that haemoglobin level has a negative correlation with serum levels of proinflammatory cytokines in this clinical group. It could be hypothesised that treatment of anaemia has anti-inflammatory effects. The aim of this study was to assess the influence of treatment with erythropoietin alpha on serum level of tumour necrosis factor alpha (TNFα) in patients with early diabetic nephropathy.

Methods
We included 36 patients with type 2 diabetes mellitus and early diabetic nephropathy (CKD stages 1–3) complicated with anaemia. Patients with nonrenal causes of anaemia and/or iron overload were not included. The main group (17 patients) received erythropoietin alpha subcutaneously (starting from 30 IU/kg with further correction of dose according to NKF-K/DOQI Guidelines, 2006) and iron medication orally (ferrous sulphate, 200 mg/day) for 16 weeks. The control group (19 patients) received only oral iron medication (ferrous sulphate, 200 mg/day) for the same period of time. Besides performing routine clinical tests we measured serum concentrations of TNFα using ELISA before and after 16 weeks of treatment. Mann–Whitney U test was used to compare mean levels of TNFα in study groups. Wilcoxon’s test was used to assess dynamics of this parameter during treatment in each group.

Results
Before treatment we found no difference in mean serum levels of TNFα in clinical groups: main group – 30.8±2.43 pg/ml, control group – 27.5±3.9 pg/ml (reference value <30 pg/ml). After 16 weeks of treatment both groups had no significant changes in concentrations of TNFα as compared to initial values. Mean serum levels of TNFα were as follows: main group – 25.0±3.6 pg/ml, control group – 31.1±4.2 pg/ml (P>0.05 for the difference between studied groups).

Conclusion
The results of the study suggest that neither treatment with iron sulphate nor comprehensive anaemia therapy with erythropoietin alpha and iron medication don’t lead to a reduction in serum concentration of TNFα in anaemic patients with early stages of diabetic nephropathy.

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Metabolic status in patients with type 1 diabetes mellitus
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Objective of the study was to analyse the relationship of compensation, lipid profile parameters and androgenic status in patients with type 1 (DM1) depending on the duration of diabetes. There were examined 76 men with DM1 aged 20–49 years (mean age 35.9±8.2) and duration of diabetes more than a year. The control group consisted of 25 healthy men aged 21–41 years (mean age 34.6±7.8). Compensation of diabetes was assessed by the level of HbA1c. Also there were assessed the lipid profile parameters (total amount of cholesterol and triglycerides), total testosterone, FSH, LH, prolactin hormone, sex hormone binding globulin, and homocysteine. Statistical analysis of the data was performed using the software package Microsoft Excel 2003 (SPSS 17.0).

It has been determined that at the absence of compensation in patients with DM1 (HbA1c 8.3±1.4%), with the increasing duration of diabetes there was noticed the increasing of BMI: a group with DM <10 years, 24.6±3.9 kg/m2, the group with DM >10 years, 27.6±4.4 kg/m2 (P=0.01), progression of lipid storage disease (increased level of triglycerides: 1.4±1.1 mmol/l vs 3.7±1.3 mmol/l in the group with DM >10 years (P=0.01)). We were not found the difference in levels of total cholesterol, LH, FSH, prolactin hormone, sex hormone binding globulin, and homocysteine. The absence of androgenic status disorders and changes of homocysteine level are probably associated with the young age of patients, a slight excess of weight and a lack of decrease in GFR. The detected changes are important risk factors of development and progression, and require appropriate arrangements, including the correction of body weight and secondary dyslipidaemia.

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The effect of exenatide treatment on serum ghrelin levels in patients with type 2 diabetes
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Aim
Ghrelin plays an important role in stimulation of food intake and long-term regulation of body weight. In present study we aimed to investigate the effect of exenatide treatment on serum ghrelin levels in patients with type 2 diabetes.

Methods
Fourteen women patients with type 2 diabetes treated with metformin and exenatide were enrolled in the study. A mixed meal test was applied to the patients while they were using their daily medications. Serum total ghrelin, glucose and insulin levels were investigated at baseline (0th min) and at the 60th, 120th, and 180th min after a mixed meal test. On the following week exenatide treatment of the patients was paused for 24 h and the same experimental procedures were repeated.

Results
Serum ghrelin levels were found suppressed significantly at the 60th and 180th min compared with baseline values after mixed meal test with exenatide treatment (P=0.042 and P=0.000 respectively). While percentage change in serum ghrelin levels after mix meal tests with and without exenatide usage were compared, no significant difference was found at the 60th and 120th min. But percent changes in serum ghrelin levels at the 180th min was statistically significant (P=0.001).

Conclusions
In present study we found that exenatide treatment suppresses serum ghrelin levels for longer time compared with the results of skipped exenatide treatment. These results suggest that the effect of exenatide on weight loss may be related with prolonged suppression of serum ghrelin levels, which is an orexigenic peptide.

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The effect of compensation of diabetes on ulcer healing in patients with diabetic foot syndrome
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Introduction
Diabetic foot syndrome is a common surgical pathology. It is the main cause of lower limb amputations, which can be avoided in 85% of cases by active detection and long-term compensation of T2DM, timely diagnostics of peripheral neuropathy.

Purpose
To study relation between compensation of diabetes (by HbA1c) and time needed for healing of ulcers and purulent processes in patients with neuroischaemic forms of diabetic foot.

Results
The results of treatment of 363 patients were worked out: 164 males (45%) and 199 females (55%), the average age of men 65±0.20 years, women 70±0.22 years (P<0.001). By admission, patients had been treated by oral hypoglycaemic medicines in combinations of up to three drugs at the time with maximum permissible doses. In hospital all subjects were treated with insulin. The most common surgery was opening of abscesses and phlegmons in 40% of males and 60% of females. Amputations of lower limbs and phalanges were performed in 40% of men (over 66 years) and 20% of women (over 70 years). In terms of post-prandial glycemia, compensation of diabetes was achieved in 22% of males and 32% of females, stay period in hospital of whom was the lowest.

Conclusions
i) With HbA1c 15.5±1.0%, duration of treatment of neuroischaemic forms of diabetic foot lasted 34.66±1.0 years, 27.6±1.0 years, 24.6±1.0 years for longer time compared with the results of skipped exenatide treatment. The effect of compensation of diabetes on ulcer healing in patients with diabetic foot syndrome was found.

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**EP454**

**Lixisenatide improves glycaemic control and body composition in uncontrolled type 2 diabetic patients treated with insulin**

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**Objective**

Evaluate the efficacy and safety of adding lixisenatide to uncontrolled type 2 diabetic (T2DM) patients treated with insulin.

**Methods**

A prospective uncontrolled study was designed. Primary endpoints (measured at 3 and 6 months) were change in HbA1c, weight, and insulin doses. Variables analysed were: HbA1c level, insulin and other hypoglycaemic agents doses, capillary glucose tests, number and type of hypoglycaemias, side effects and body composition analysis (Tanita SC-330).

**Results**

Data from 42 T2DM patients (55% women; mean age: 57.7 ± 7.4 years; and T2DM duration: 13.5 ± 8.7 years) treated with lixisenatide were analysed. A significant decrease in HbA1c levels (7.6 ± 0.8% vs 7.8 ± 1.1% vs 7.3 ± 1.6%; P < 0.001) and weight (95.2 ± 14.8 kg vs 95.8 ± 14.4 kg vs 98.5 ± 13.9 kg) was observed at 3 and 6 months compared to baseline and % of fat mass had also reduced at 6 months (33.9 ± 7.6% vs 38.8 ± 8.0% vs P < 0.01). Total insulin doses decreased from baseline (61.2 ± 37.3 U/day) to 3 (52.5 ± 34.8 U/day; P < 0.02) and 6 months (49.4 ± 30.5 U/day; P < 0.02). Low incidence of no serious hypoglycaemias (1.0 ± 1.7 mean episodes/month) was referred. Six patients (14.3%) discontinued lixisenatide treatment due to side effects (four patients for nausea or vomiting, one patient for hypertransaminasemia, and one patient for uncontrolled hyperglycaemia). Three patients (7.1%) were lost to follow-up for unknown reasons.

**Conclusions**

In our clinical experience, lixisenatide contributes to improving glycaemic control as facilitates weight loss and insulin doses reduction in T2DM patients uncontrolled with insulin.

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**EP455**

**Liraglutide improves β-cell function, measured by the C-peptide/glucose ratio, in obese patients with type 2 diabetes**

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**Introduction**

β-cell function declines progressively in patients with type 2 diabetes (T2D), the fasting C-peptide/glucose ratio (Cp/G) is used for its evaluation. The GLP1 receptor agonist liraglutide improves glucose and weight control, presumably due to improvement of β-cell function and/or mass. This study evaluates the effect of 6-months’ treatment with liraglutide in β-cell function, measured by Cp/G, in patients with obesity and T2D.

**Materials and methods**

We analysed 43 patients (24 women) with orally treated T2D and obesity, to assess serum Cp/G. Patients previously received one oral-hypoglycemic-agent (OHA), and the rest, two. At 6 months compared to baseline and % of fat mass had also reduced at 6 months (33.9 ± 7.6% vs 38.8 ± 8.0% vs P < 0.01). Total insulin doses decreased from baseline (61.2 ± 37.3 U/day) to 3 (52.5 ± 34.8 U/day; P < 0.02) and 6 months (49.4 ± 30.5 U/day; P < 0.02). Low incidence of no serious hypoglycaemias (1.0 ± 1.7 mean episodes/month) was referred. Six patients (14.3%) discontinued lixisenatide treatment due to side effects (four patients for nausea or vomiting, one patient for hypertransaminasemia, and one patient for uncontrolled hyperglycaemia). Three patients (7.1%) were lost to follow-up for unknown reasons.

**Conclusions**

In our clinical experience, lixisenatide contributes to improving glycaemic control as facilitates weight loss and insulin doses reduction in T2DM patients uncontrolled with insulin.

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**EP456**

**Study of irisin hormone level in type 2 diabetic patients with and without diabetic neuropathy**

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**Background and aims**

Irisin is a novel myokine that promote energy expenditure. It could act on adipocyte metabolism through a novel neural pathway and on the other hand irisin induces neural proliferation and adequate neural differentiation. We aimed to assess serum irisin level in type 2 diabetics (T2DM) and correlate it with metabolic parameters. Also, we assessed the relation between irisin level and diabetic peripheral neuropathy (DPN).

**Methods**

We recruited 60 T2DM subjects and 30 healthy controls. Diabetics will be divided into 30 patients without complications and 30 with DPN. DN4 questionnaire was used to screen for diabetic neuropathy. Serum irisin, FPG, 2 h PG, HbA1c, fasting insulin, and HOMA-IR were measured.

**Results**

Irisin level was significantly lower in diabetics than control (40.92 ± 17.99 ng/ml vs 160.14 ± 58.67 ng/ml, P < 0.01). Diabetics with PN had lower irisin than diabetics without complications (27.57 ± 7.61 ng/ml vs 54.27 ± 15.24 ng/ml, P < 0.01). Irisin levels were negatively correlated with FBS (r = −0.487), 2 h PG (r = −0.570), HbA1c (r = −0.596), fasting insulin (r = −0.368), HOMA-IR (r = −0.441), and TGs (r = −0.327) in all studied groups (P < 0.01). Also, it was negatively correlated with the duration of diabetes in all diabetics (r = −0.764, P < 0.01). We found a negative correlation between irisin and age only in healthy subjects (r = −0.480, P < 0.01). Multiple regression analysis revealed that Hba1c, age, F. Insulin, BMI, and HOMA-IR respectively were independent determinants for irisin level.

**Conclusion**

We found that serum irisin levels were decreased in T2DM. Lower irisin level may be associated with peripheral neuropathy. Irisin levels associated inversely with insulin resistance.

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**EP457**

**Clinical experience with lixisenatide in patients with obesity and type 2 diabetes**

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**Introduction**

Agonist-receptor-GLP1 (AR-GLP1) had demonstrated its utility in obese patients with diabetes type 2. Since August 2013 we have available in Spain a new AR-GLP1 with prandial action in a single daily dose, lixisenatide. There are different clinical trials that support its efficacy and security but the dates from real clinical practice are scarce.

**Aim**

To analyse the efficacy and security in real clinical practice for the treatment of diabetes type 2 patients with BMI ≥30 kg/m2 in a 12 months period.

**Materials and methods**

Data from patients attending in an Endocrinology Unit from two Spanish centres were collected in a retrospective way (n = 77). Initially, during 7 days patients received lixisenatide 10 µg in single dose and later, they received the maintenance dose of lixisenatide 20 µg. Primary endpoint was change in HbA1c from baseline.
Body weight, adverse effects and other treatment for diabetes were collected. Available data were analysed with SPSS 20.

Results

77 obese (32 males, age 58.02 ± 12.5 years old) and type 2 diabetic patients (mean weight 94.53 kg, mean duration of diabetes 7.1 years, and mean HbA1c 9.01%). Data at 12 months of treatment were analysed. In this period, the HbA1c decreased −1.04 ± 0.29% (P < 0.001) and the body weight decreased 6.26 ± 2.56 kg (P = 0.01). Insulin was discontinued in 12.5% of the patients, mean initial dose 44 IU, mean final dose 29 IU, P = 0.01. Mild transient gastrointestinal side effects were experimented by 8%. Three patients discontinued treatment (vomiting and refusing s.c. injection).

Conclusions

In our study, the efficacy of lixisenatide had been superior that reported in clinical trials in both aspects, HbA1c control and weight lost. In addition, this treatment had reduced the insulin requirements. Side effects are infrequent and mostly mild. More studies are necessary to support our results.

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**EP458**

Controlled attenuation parameter have close relationship with the prevalence and the severity of non-alcoholic fatty liver disease in a type 2 diabetes mellitus population

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Background

The severity of non-alcoholic fatty liver disease (NAFLD) in type 2 diabetes mellitus (T2DM) population compared with that in normal glucose tolerance (NGT) individuals has not yet been assessed by a quantitative method. We investigated the prevalence and the severity of NAFLD in a T2DM population using controlled attenuation parameter (CAP).

Methods

Subjects who underwent testing for biomarkers related to T2DM and CAP using Fibroscan during a regular health check-up were enrolled. CAP values of 250 and 300 dB/m were selected as the cutoffs for the presence of NAFLD and for moderate to severe NAFLD respectively. Biomarkers related to T2DM included fasting glucose/insulin, C-peptide, HbA1c, glycoalbumin, and HOMA-IR.

Results

Among 340 study participants (T2DM, n = 66; pre-diabetes, n = 202; and NGT, n = 72), the proportion of subjects with NAFLD increased according to the glucose tolerance status (31.9% in NGT, 47.0% in pre-diabetes; and 57.6% in T2DM). The median CAP value was significantly higher in subjects with T2DM (265 dB/m) than in those with pre-diabetes (245 dB/m) or NGT (231 dB/m) (all P < 0.05). Logistic regression analysis showed that subjects with moderate to severe NAFLD had a 2.4-fold (odds ratio) risk of having T2DM than those without NAFLD (P = 0.02; 95% CI 1.13–4.86), and positive correlations between the CAP value and HOMA-IR (r = 0.407) or C-peptide (r = 0.402) were demonstrated.

Conclusion

Subjects with T2DM had a higher prevalence of severe NAFLD than those with NGT. Increased hepatic steatosis was independently associated with the presence of T2DM, and insulin resistance induced by hepatic fat may be an important mechanistic connection.

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**EP459**

Risk factors, aetiology, and prognosis in patients with ischaemic stroke and diabetes mellitus

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Objective

To describe the clinical, aetiological and prognostic differences in diabetic and non-diabetic ischaemic stroke (IS) patients.

Materials and methods

Retrospective analysis of prospective series of IS patients. Patients were classified as non-DM and DM patients. Demographic and clinical characteristics were compared between two groups. IS prognosis was evaluated by modified Rankin scale (mRS) and NIHSS (NIH stroke scale).

Results

138 were included (53 diabetic and 71 non-diabetic). Mean age was 73.95 (± 14.43) years in DM patients and 74 (±11.51) in non-DM. The prevalence of hypertension (88.6% vs 66.9%, P < 0.005), hypercholesterolemia (56.6% vs 33.8%, P < 0.05), coronary artery disease (15% vs 8.4%, P = 0.18), peripheral artery disease (3.7% vs 2.8%, P = 0.76), previous stroke (33.9% vs 15.4%, P < 0.05), and atrial fibrillation (16.9% vs 9.8%, P = 0.24) was higher in DM patients compared to non-DM patients. Smoking habit was more common among non-DM patients (15.4% vs 7.5%, P = 0.13). Stroke subtype distribution didn’t differ between two groups: Atherothrombotic etiology (18.8% in DM patients vs 14% in non-DM patients), cardioembolic (24.5% vs 28.1%), lacunar (20.7% vs 18.3%), and undetermined (35% vs 39.4%). The prevalence of transient ischaemic attack was higher among non-DM patients (33.8% vs 22.6%, P = 0.19). There were no differences in stroke severity between DM patients and non-DM patients. mRS 0–2 at discharge prevalence was 74.5% vs 76%, P = 0.94. NIHSS ≥ 8 was 25% vs 21.1%, P = 0.49 respectively.

Conclusions

Our study reveals a higher prevalence of other vascular risk factors in diabetes patients. We have found no differences in relation to IS subtype and IS prognosis.

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**EP460**

Establishing the relationship between third-trimester foetal abdominal circumference, birthweight, and neonatal morbidity in gestational diabetes

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Introduction

Gestational diabetes (GD) is associated with a significantly higher risk of perinatal complications. It has been suggested that third-trimester (3thT) foetal abdominal circumference (AC) determination is an important predictor of macrosomia and large for gestational age (LGA).

Aims

The purpose of this study was to evaluate the association between the 3thT AC percentile with birthweight (BW) and adverse neonatal outcomes in a cohort of women with GD.

Methods

We retrospectively analysed the AC percentile of the 3thT ultrasound screening in pregnant women with GD within a 2 years period in a Central University Hospital. We enrolled 268 pregnant women with singleton pregnancy undergoing routine fetal biometry after 28 weeks. The relationship between AC and BW was explored using the Spearman’s correlation and among AC percentile groups (<50, ≥50) and adverse neonatal outcomes using the Fisher’s exact test.

Results

The study included 268 singleton pregnancies; the median maternal age was 33 years old (range, 17–52) with a median delivery week of 39 weeks (range, 29–41). The median BW was 3165 g (range, 1370–4450), 3thT ultrasound gestational age measurement 36 weeks (range, 29–40) and AC percentile 50 (range, 1–100). Neonatal outcomes prevalences: neonatal morbidity compositum (n = 67; 25%), small for gestational age (n = 25; 9.3%), LGA (n = 24; 9.0%), macrosomia (n = 12; 4.5%), and neonatal hypoglycaemia (n = 5; 1.9%). The macrosomia and LGA rates were greater in the AC percentile group ≥50 compared to <50 (91.7% vs 83.5% and 95.8% vs 4.2% respectively) (P < 0.05). There was no significant difference in neonatal hypoglycaemia rate between groups (80% vs 20%, P = 0.384). We documented a strong positive correlation between AC and BW: R² = 0.626, P < 0.001 (R² = 0.392).

Conclusions

The intrapartum AC measurement was useful in screening fetal macrosomia and LGA. These results suggest that AC measured by ultrasound can help to predict the BW and seems to be a valuable parameter to be included when we evaluate a gestational diabetic pregnant woman.

DOI: 10.1530/endoabs.37.EP460
Carotid intima-media thickness (IMT) has been shown an independent predictive marker of coronary artery disease (CAD) and cardiovascular disease in many studies. We investigated the usefulness of carotid IMT as a screening test for CAD in Korean diabetic patients. We conducted retrospective study and found the type 2 diabetic patients without cardiovascular disease history who underwent carotid ultrasonography (US) and stress echocardiography (SE) from June 2006 to December 2012 at Kyung Hee University Hospital at Gangdong, Seoul, Republic of Korea; Department of Endocrinology and Metabolism, Korea University Guro Hospital, Seoul, Republic of Korea.

Methods

In the present study 60 NIDDM patients on oral hypoglycaemic drugs were randomly divided into two groups; 30 subjects (11 males and 19 females) were supplemented with the juice of *A. marmelos* fresh leaves (20 g/100 ml) every morning empty stomach for 60 days against 30 (14 males and 16 females) subjects taking into carotid US results with SE results, they improved positive predictive value in significant CAD.

Results

52 of 218 patients underwent coronary angiography. 32 of 52 patients had positive SE and positive predictive value of SE in significant CAD was 84.4% (27 of 32 patients). Of 32 patients with positive SE, 16 patients had carotid plaque and all of them had significant CAD. In conclusion, carotid US abnormalities alone had limitation to correlated SE results and predict significant CAD. However, when taking into carotid US results with SE results, they improved positive predictive value in significant CAD.

Disclosure

U. JSK.

DOI: 10.1530/endoabs.37.EP461

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Methods

In the present study 60 NIDDM patients on oral hypoglycaemic drugs were randomly divided into two groups; 30 subjects (11 males and 19 females) were supplemented with the juice of *A. marmelos* fresh leaves (20 g/100 ml) every morning empty stomach for 60 days against 30 (14 males and 16 females) subjects taking into carotid US results with SE results, they improved positive predictive value in significant CAD.

Results

52 of 218 patients underwent coronary angiography. 32 of 52 patients had positive SE and positive predictive value of SE in significant CAD was 84.4% (27 of 32 patients). Of 32 patients with positive SE, 16 patients had carotid plaque and all of them had significant CAD. In conclusion, carotid US abnormalities alone had limitation to correlated SE results and predict significant CAD. However, when taking into carotid US results with SE results, they improved positive predictive value in significant CAD.

Disclosure

U. JSK.

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Beneficial effects of antioxidant property of *Aegle marmelos* leaves serum antioxidant status on blood glucose levels in diabetes type 2 subjects

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Background

Diabetes mellitus is one of the most recognized and clinically significant disorders of the endocrine system. Based on recent advances and involvement of oxidative stress in complicating diabetes mellitus, efforts are on to find suitable anti diabetic and antioxidant therapy. *Aegle marmelos* (L.) Corr. is one of the most important Indian medicinal plants which has enormous traditional values against various diseases and many bioactive compounds have been isolated from this plant.

Methods

In the present study 60 NIDDM patients on oral hypoglycaemic drugs were randomly divided into two groups; 30 subjects (11 males and 19 females) were supplemented with the juice of *A. marmelos* fresh leaves (20 g/100 ml) every morning empty stomach for 60 days against 30 (14 males and 16 females) subjects as controls. The ‘antioxidant power’ of the serum (ferric reducing ability of plasma), was taken as the indicator of total antioxidant potential.

Results

Supplementation of the juice significantly (P < 0.0001) decreased fasting blood glucose and HbA1c levels and significant (P < 0.0001) increase in serum antioxidant activity (serum FRAP), Whereas significant (P = 0.008) increase in fasting blood glucose levels and significant decrease in serum antioxidant activity (P < 0.0001) was observed for control.

Conclusion

The present study proves the antidiabetic activity of the *A. marmelos* leaves. We believe antioxidant therapy along with monitoring of host antioxidant defences would definitely help in blocking the effects of oxidative stress. We propose that *A. marmelos* leaf juice as an antioxidant therapy monitored with the help of FRAP assay along with oral hypoglycaemic drugs can control blood glucose to normal levels in patients whose diabetes is not controlled with these agents or produce adverse effects on dose increments.

Disclosure


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Occurrence frequency of diabetic foot syndrome in three pilot regions of Uzbekistan

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Goal

To study occurrence frequency of diabetic foot syndrome (DFS) in three pilot regions of Uzbekistan.

Material and methods

Upon WDF project, ‘UMID’ Association of Tashkent and RRPMCE have screened T1DM and T2DM patients for DFS in three pilot regions (Andizhan, Tashkent, and Kashkadarya areas). 663 patients examined: of them 581 T2DM patients and 82 T1DM peoples in the 25–65 age groups with duration of the disease 5–15 years. Results of UPI Doppler velocimetry, levels of glycemia, HbA1c, cholesterol, HDL, LDL, and triglycerides were studied.

Results

83.2% of T2DM and 67.4% of T1DM had diabetic polyneuropathy. Frequency of DFS occurrence was 55.3% (T2DM) and 31.7% (T1DM) accordingly. The greatest number of lower limb amputations (3.8%) and re-amputations (2.0%) was found in T2DM patients with disease of 7–10 years. Results of interviews

Disclosure


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Male patients benefit from initial exenatide treatment: a real-world experience

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Objective

The purpose of this study was to describe the outcome after initiation of exenatide therapy and to determine whether the impact of adverse drug reactions on compliance was affected by gender.

Methods

A retrospective study was performed of 18 diabetic patients (eight males) that were prescribed exenatide between June 2013 and September 2014. Each included patient received exenatide for ≥1 month. Age, disease course, race, BMI, medical history, chronic complications associated with diabetes, and the state of pretreatment glycemic control were analyzed. Both 1 and 4 weeks after treatment, data such as blood glucose, blood lipids, and body weight were collected to determine any adverse drug reactions and the impact of gender on exenatide withdrawal.

Results

The incidence of adverse drug reaction was significantly higher in females than male patients following exenatide treatment (P < 0.05). Although there was no significant difference between the male and female group 1 week, adverse drug reactions continued longer in females and the incidence of adverse drug reaction was significantly higher in female patients 4 weeks after initiating treatment (P < 0.01). As a result, four female patients stopped the medication, whereas only one male patient stopped taking the medication because the patient was unaccustomed to the drug injection process. The efficacy of exenatide was similar between the two groups at both 1 and 4 weeks.

Conclusion

Exenatide, a glucagon-like peptide 1 agonist often causes relatively significant gastrointestinal reactions during its initial application. Gender difference in adverse drug reactions may be due to the impact of this drug on the feeding centre in the CNS.

Disclosure


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pertaining to rules of foot care showed a poor knowledge on DFS prevention which explains a rise in a number of amputations in PDM in rural regions. 94.2% of PDM were in a decompensation stage (HbA1c > 9.5%) irrespective of history of the disease, 68% of PDM were hypertensive. 36% of PDM (mostly T2DM patients with obesity grades 1 and 2) had high levels of cholesterol and LDL (5.6±2.07 and 4.01±0.12 mmol/l respectively) with low level of HDL (0.53±0.05 mmol/l) and level of triglycerides of 2.8±0.3 mmol/l.

Conclusions
i) Frequency of DFS occurrence in three pilot regions of Uzbekistan made 55.3% in T2DM patients and 31.7% in those of T1DM; ii) the greatest number of lower limb amputations (3.8%) and re-amputations (2.0%) was found in T2DM patients with duration of the disease 7–10 years; and iii) decompensation stage (HbA1c > 9.5%) in 94.2% of PDM is one of principal causes of high frequency of DFS occurrence and a considerable number of amputations in PDM.

Disclosure
World Diabetes Foundation grant number 08-379, dd 07.09.2009.


EP465
Nocturnal blood pressure is related to the progression of retinopathy in type 1 diabetic patients
Francisco Javier Vílchez-López1, Isabel Mateo-Gavira1, Laura Larrán-Escandón1, Ana Montero-Galván1, José Ortego-Rojo1, María Victoria García-Palacios2 & Manuel Aguilar-Diosdado1
1Endocrinology, Puerta del Mar Hospital, Cádiz, Spain; 2Preventive Medicine and Public Health, Cádiz, Spain.

Introduction
The objective is to evaluate the relationship between early blood pressure alterations (detected by ambulatory blood pressure monitoring (abpm)) and the development/progression of retinopathy in patients with type 1 diabetes clinically normotensive.

Methods
We designed a prospective observational study of 85 patients, clinically normotensive and without microalbuminuria, monitored over 7 years. Abpm was performed over 24 h and subclinical hypertension was considered if: i) mean systolic pressure (sbp) was > 130 mmHg in the 24 h and daytime periods and > 120 mmHg in the nighttime period and/or mean diastolic pressure (dbp) > 80 or 70 mmHg in the same periods respectively and/or ii) more than 50% of the readings were higher than the defined previous criteria. Non dipper pattern was defined as nocturnal sbp or dbp < 10% relative to the diurnal mean value. We evaluated the development or progression of retinopathy during the following period.

Results
Of the 85 patients included in the analysis, 55.3% (n = 47) were women with an average age of 27.9±6.1 years and a length of disease of 12.3±6.5 years. 23.5% were diagnosed with subclinical hypertension and 36% with non-dipper pattern as the only pathological finding. 69 patients completed the 7-year study. During this period: i) 10.14% developed microalbuminuria, showing the mean nocturnal sbp as a risk factor (OR: 1.129, P = 0.007) and ii) 7.24% of the normotensive patients progressed to established hypertension, showing historical HbA1c (OR: 2.767, P = 0.046) and mean nocturnal dbp (OR: 1.243, P = 0.046) as related factors.

Conclusions
In type 1 diabetic patients clinically normotensive with normalalbuminuria, nocturnal blood pressure parameters predispose the development of microalbuminuria and established hypertension.

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EP466
Nocturnal blood pressure is related to the development of microalbuminuria and established hypertension in patients with type 1 diabetes
Francisco Javier Vílchez-López1, Isabel Mateo-Gavira1, Laura Larrán-Escandón1, Ana Montero-Galván1, José Ortego-Rojo1, María Victoria García-Palacios2 & Manuel Aguilar-Diosdado1
1Endocrinology, Puerta del Mar Hospital, Cádiz, Spain; 2Preventive Medicine and Public Health, Puerta del Mar Hospital, Cádiz, Spain.

Introduction
The objective is to evaluate the relationship between early blood pressure alterations (detected by ambulatory blood pressure monitoring (abpm)) and the development of microalbuminuria and arterial hypertension in patients with type 1 diabetes clinically normotensive.

Methods
We designed a prospective observational study of 85 patients, clinically normotensive and without microalbuminuria, monitored over 7 years. Abpm was performed over 24 h and subclinical hypertension was considered if: i) mean systolic pressure (sbp) was > 130 mmHg in the 24 h and daytime periods and > 120 mmHg in the nighttime period and/or mean diastolic pressure (dbp) > 80 or 70 mmHg in the same periods respectively and/or ii) more than 50% of the readings were higher than the defined previous criteria. Non dipper pattern was defined as nocturnal sbp or dbp < 10% relative to the diurnal mean value. We evaluated the development of microalbuminuria and established hypertension during the following period.

Results
Of the 85 patients included in the analysis, 55.3% (n = 47) were women with an average age of 27.9±6.1 years and a length of disease of 12.3±6.5 years. 23.5% were diagnosed with subclinical hypertension and 36% with non-dipper pattern as the only pathological finding. 69 patients completed the 7-year study. During this period: i) 7.24% of the normotensive patients progressed to established hypertension, showing historical HbA1c (OR: 2.767, P = 0.046) and mean nocturnal dbp (OR: 1.243, P = 0.046) as related factors.

Conclusions
In type 1 diabetic patients clinically normotensive with normalalbuminuria, nocturnal blood pressure parameters predispose the development of microalbuminuria and established hypertension.


EP467
Subclinical blood pressure alterations are related to proinflammatory markers in type 1 diabetes mellitus
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Introduction
The objective is to evaluate the relationship between precocious subclinical hypertension and inflammatory and endothelial dysfunction markers in normotensive and normalalbuminuria patients with type 1 diabetes.

Methods
We designed an observational transversal study of 85 patients, clinically normotensive and without microalbuminuria. Ambulatory blood pressure monitoring (abpm) was performed over 24 h and subclinical hypertension was considered if: i) mean systolic pressure (sbp) was > 130 mmHg in the 24 h and daytime periods and > 120 mmHg in the nighttime period and/or mean diastolic pressure (dbp) > 80 or 70 mmHg in the same periods respectively and/or ii) more than 50% of the readings were higher than the defined previous criteria. Non dipper pattern was defined as nocturnal sbp or dbp < 10% relative to the diurnal mean value. We analyzed the relationship between the blood pressure alterations detected by abpm and inflammatory cytokines (IL6, TNFα, and VEGF) and markers of endothelial damage (VCAM, ICAM, and PAI).

Results
Of the 85 patients included in the analysis, 55.3% (n = 47) were women with an average age of 27.9±6.1 years and a length of disease of 12.3±6.5 years. 31.8% presented subclinical hypertension and 36% with non-dipper pattern as the only pathological finding. The readings were higher than the defined previous criteria. VEGF levels were significantly higher in patients with diurnal blood pressure alterations relative to normotensive patients (112.33 (72.87–213.53) pg/ml vs 71.03 (37.71–107.92) pg/ml; P = 0.007). In addition, VEGF levels showed a significant correlation with mean daytime and 24 h blood pressure parameters. IL6 levels showed as a risk factor in patients diagnosed with subclinical hypertension (OR: 1.406, P = 0.027). There were no modifications in the level of markers of endothelial damage.

Conclusions
An increase in proinflammatory cytokines, although not markers of endothelial damage, exists in precocious stages of hypertension in type 1 diabetic patients.

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**EP468**

**Different stress hormone response in insulin pump treatment compared with multiple daily injection: preliminary data**

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It is known that in type 1 diabetes mellitus (T1DM) continuous subcutaneous insulin infusion (CSII) therapy improves metabolic control and reduces risk of hypoglycaemia in comparison with multiple daily injection (MDI). Metabolic outcomes usually considered are HbA1c, BMI, and inflammatory parameters. However few data are available on pituitary and gonadal hormone responses, which are involved in metabolic processes. In order to study the response of anabolic hormones in patients treated with CSII or MDI, we have evaluated IGF1, DHEAS, and testosterone levels in a cohort of T1DM patients, comparing these two different ways of intensive insulin administration. We enrolled 41 patients, aged 19–55 years, 25 males and 16 females; 23 were treated by MDI (group 1) and 18 by CSII (group 2). The groups were similar for age, BMI, and duration of DM. IGF1 was assayed using the electro-chemiluminescent immunoassay (ECLIA) method instead testosterone and DHEAS using the chemiluminescent microparticle immunoassay (CMIA) method. Despite similar glycaemic control (mean ± s.d., HbA1c: 8.2 ± 0.01 in males and 7.2 ± 0.01 in females of group 1; 7.7 ± 0.01 both in males and females of group 2), we found in males a significant difference in IGF1 levels (138.8 ± 9.4 in group 1 and 96.2 ± 11.2 ng/ml in group 2, P < 0.05) and a not significant trend toward higher DHEAS levels (2912.2 ± 432.9 and 1989.6 ± 216.9 ng/ml); T levels were higher in females of group 1 than group 2 (12.2 ± 0.8 and 0.5 ± 0.1 ng/ml).

These preliminary data seem to indicate a different hormone response in patients treated by CSII or MDI, with lower stress hormone pattern response for patients on CSII, despite similar glycaemic control. Better ovarian response was observed in women on CSII, with lower androgen production. Further studies are needed to better understand these complex relationships and their prognostic implications.

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**EP469**

**Evaluating analogue vs human insulin efficacy in real life: observational study in 2 Albanian diabetic patients, previously insulin treated**

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Background and aims

Insulin therapy is an important part of diabetes treatment. A lot of studies have compared the efficacy of new insulin therapies, but in our country, specialists still have to demonstrate at the institutions the treatment’s efficacy and cost-effectiveness for new insulin analogues. The aims of our study is to evaluate the efficacy of analogues vs human insulins and differences between various analogue insulin, in type 2 diabetes patients, previously treated with human insulin.

Methods

This study is realised in real life patients. We retrospectively included 384 patients, previously treated ≥24 months with human insulins, switched to an analogue insulin for ≥12 months. Treatment efficacy was evaluated by HbA1c levels, weight difference and changes in total daily dose (TDD) analogue vs human.

Results

384 patients, 185 (48.17%) males. Glargine 194 (50.5%), detemir 110 (28.65%), and all other analogs (AAOA) 80 (20.85%). Mean age 62.19 (s.d. 10.12) years, mean diabetes duration 10.8 (s.d. 5.35) years. Mean duration on analogue insulin therapy was 19.1 months. Overall mean HbA1c was 8.86 (s.d. 1.06) vs 7.51 (s.d. 0.91) in group 1 and 96.2 in group 2, K < 0.01 in males and 7.9 in group 1 and 9.4 in group 2,

2(1.2 0.01 in males and 0.05) and a not significant trend toward higher DHEAS levels (2912

216.9 ng/ml); T levels were higher in females of group 1 than group 2 (12.2 ± 0.8 and 0.5 ± 0.1 ng/ml).

These preliminary data seem to indicate a different hormone response in patients treated by CSII or MDI, with lower stress hormone pattern response for patients on CSII, despite similar glycaemic control. Better ovarian response was observed in women on CSII, with lower androgen production. Further studies are needed to better understand these complex relationships and their prognostic implications.

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**EP470**

**Telemedicine as a motivational tool to optimise metabolic control in patients with diabetes in Turkey: results from a randomised controlled trial**

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Objective

Our purpose was to evaluate the impact of a transmission system on metabolic control of patients with diabetes.

Research design and methods

This ongoing prospective, randomized, comparative study included adult patients with type 1 (n = 71) and type 2 diabetes (n = 139). Consecutive patients were equally allocated into two groups. Both groups received routine care by the same health care professionals (HCPs) 3-monthly. TeleDiab group additionally transmitted SMBG data and received feedbacks and SMSs regularly.

Results

We reviewed metabolic parameters based on mean difference from baseline to 9 months. In TeleDiab group, fasting blood glucose (FBG: −19 mg/dl, P = 0.089), Hba1c (0.6%, P < 0.001), HDL-cholesterol (−3.6 mg/dl, P = 0.006), systolic (SBP: −5.3 mmHg, P = 0.001), and diastolic blood pressures (DBP: −2.7 mmHg, P = 0.055) remarkably reduced from baseline. While in control group Hba1c (−0.4%, P = 0.004) only reduced but BMI (0.6 kg/m², P = 0.014) increased significantly; additionally, SBP (−2.8 mmHg, P = 0.099) and DBP (−2.4 mmHg, P = 0.079) tended to decrease tended to increase from baseline.

In TeleDiab group, we observed positive correlations between average number of SMBG and change from baseline to 9 months FBG (monthly post-prandial: r = 0.256, P = 0.029) and weight (daily post-prandial: r = 0.229, P = 0.049); and negative correlations between average number of SMBG and change from baseline to 9 months HDL-cholesterol (daily postprandial: r = −0.261, P = 0.026), SBP (weekly total: r = −0.278, P = 0.017; weekly pre-prandial: r = −0.233, P = 0.046; monthly total: r = −0.272, P = 0.019; monthly pre-prandial: r = −0.247, P = 0.034; and monthly post-prandial: r = −0.247, P = 0.035), and DBP (weekly post-prandial: r = −0.284, P = 0.044; monthly total: r = −0.234, P = 0.044; and monthly post-prandial: r = −0.316, P = 0.006).

At 9-month, more patients with type 2 diabetes in TeleDiab group achieved optimal Hba1c as compared with control group (52.1% vs 38.3%, P = 0.001).

Conclusion

Regular follow-up visits by the same HCPs resulted with improved glycaemic, lipid and BP control in subjects with diabetes. However, further improvement was achieved with the use of electronic transmission system.

Disclosure

This work is partly supported by Turkcell Telecommunication Company (2004/2012).

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**EP471**

**Long-term tele-monitoring of patients with type 2 diabetes mellitus: ancillary analysis of the results of the Greek pilot of the renewing health multicentre randomised control trial**

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Introduction

To evaluate the impact of a long-term telemonitoring programme for patients with type 2 diabetes mellitus (DMTZ) on glycaemic control and lipid disorders.

Methods/design

In the Greek pilot of a prospective, randomised, single-blinded, multicentre study (154 patients with DMT2, Hba1c > 53 mmol/mol (7.0% according to NGSP) and capable of using the telemonitoring device, were studied after randomly assigned in the telemonitoring (IG) (n = 74) and the control group (CG) (n = 80) and after having signed the informed consent form. In the IG group patients’ blood glucose
profiles were collected weekly using a mobile phone health platform, for a period of 1 year. Allocated health professionals provided via phone the appropriate counselling on lifestyle and medication changes whenever required. Patients in (CG) group received usual care with face-to-face consultations. Levels of HbA1c (primary outcome), total cholesterol (TChol), LDL, and triglycerides (Tg) were measured at the beginning and the end of the study.

Results
The table shows the outcome of the variables studied in both groups. A greater reduction in HbA1c was observed in the IG compared to the CG. Linear regression analysis performed proved that no significant contribution to the reduction of HbA1c level could be attributed to patients’ demographics, age ($R^2=0.099$, $P=0.103$), gender ($R^2=0.061$, $P=0.316$), level of education ($R^2=0.034$, $P=0.572$), prior use of computer ($R^2=0.062$, $P=0.309$), and prior use of mobile phone ($R^2=0.005$, $P=0.406$).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean difference between groups (95% CI)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>$-6.13 (-10.45$ to $-1.81)$</td>
<td>0.001</td>
</tr>
<tr>
<td>TChol (mg/dl)</td>
<td>$-2.41 (-18.48$ to $13.65)$</td>
<td>0.765</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>$-6.72 (-16.02$ to $2.57)$</td>
<td>0.155</td>
</tr>
<tr>
<td>Tg (mg/dl)</td>
<td>$-12.90 (-49.97$ to $24.17)$</td>
<td>0.400</td>
</tr>
</tbody>
</table>

Conclusion
In the present study home telemonitoring was proven to be more effective than usual care in improving glycaemic control.

Disclosure
RENEWING HEALTH and UNITED FOR HEALTH are partially funded under the ICT Policy Support Programme (ICT PSP) as part of the Competitiveness and Innovation Framework Programme by the European Community.

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**EP472**

Is diabetes an independent risk factor of perioperative complications after abdominal gynecologic interventions?

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Purpose
We sought to determine if in the group of patients who underwent gynecologic abdominal interventions diabetes was an independent risk factor of perioperative complications.

Material and methods
The study group included 62 women from both the diabetic and the control group who underwent elective gynecologic laparotomies such as hysterectomy or adnexectomy. The patients from diabetic group were pair-matched with patients without diabetes based on the following criteria: similar age and BMI, the same gynecologic diagnosis, undergoing the same type of gynecologic surgery, operation being performed on in the same operating room and hospitalization within the same time interval. In every matched couple of patients (diabetic vs non-diabetic patient) we compared: number and characteristics of intra- and postoperative complications, postoperative length of stay in hospital, decrease in hemoglobin level, increase in body temperature and postoperative use of antibiotics.

Results
The study did not show any statistically significant differences between the diabetic patients and corresponding patients from the control group in terms of the examined parameters.

Conclusion
Diabetes was not an independent risk factor of early postoperative complications after abdominal adenexectomies and hysterectomies in the examined group of patients. Good pre-operative glycemic control and keeping blood glucose in intra and postoperative time within normal ranges results in the reduction of complications in diabetic patients to the level typical of non-diabetics.

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**EP473**

Education for diabetes self-management improves quality of life and reduces HbA1c levels in people with diabetes

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Backgrounds and aims
Knowing about patient’s quality of life (QoL) is becoming increasingly important in delivering diabetes care and education. The purpose of our study was to estimate if the diabetes education improves patient QoL and reduces HbA1c levels.

Material and methods
The study sample included diabetic patients who attended a 5-day educational sessions at the Service of Endocrinology in Tirana/Albania. Patients were evaluated regarding their QoL at baseline and 6 or 12 months after their hospitalization. The HbA1c was measured at baseline, 6 and 12 months later. The diabetes QoL (DQoL) measure was used to assess the subjective QoL. DQoL is a validated 46 items survey covering four areas of interest: satisfaction and impact of treatment, worry about the future effects of diabetes and worry about social issues, as well a single question about the general health. A satisfactory level is accepted as a transformed score $>60$.

Results
The group consisted of 395 patients, 139 males (35%) and 256 females, 97 (24.5%) type 1 diabetes, mean age 44.2 ± 4.7 years, diabetes duration 11.4 ± 5.4 years, treated with insulin in 45% of cases, with baseline HbA1c 9.1 ± 1.67%, having decreased respectively 8.5 ± 1.1% at 6 months ($P<0.05$) and 8.02 ± 1.23% at 12 months after hospitalization ($P<0.001$). DQoL at baseline was 56 ± 4.5, 68.2 ± 5.7 at 6 months later and 75.1 ± 3.5 at 12 months interval ($P<0.05$). The satisfaction with treatment and worry about the future were the most improved scores at 6 and 12 months after.

Conclusions
The education for self-management of the disease improves patients’ QoL as well their metabolic control.

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**EP474**

Prevalence of microalbuminuria and predictive factors in a group of Albanian diabetic adults

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Background and aims
Diabetic nephropathy is one of the most prevalent and dangerous chronic complication of diabetes mellitus. Its end-stage, renal chronic failure is the most important cause of premature death in diabetic patients. Microalbuminuria (MA), one of the first signs of diabetic nephropathy, may be present from the moment of diagnosis in type 2 diabetes. The aim of our study was to determine the prevalence of microalbuminuria and to identify preditor factors in a group of Albanian diabetic adult patients.

Material and methods
Diabetic patients selected randomly, assigned by hospital admissions in Tirana University Hospital Center, Shkodra and Pogradec regional hospitals. Biochemical examinations, anthropometric measurements, and measurement of microalbuminuria by DCA 2000 in a urine spot, was performed. Microalbuminuria was considered positive if ≥ 20 mg or albumine/creatinine report ≥ 25.

Results
321 patients participated in the study. 163 women (50.78%). The mean age 58.21 ± 11.87 years, type 1 diabetes 19 patients (8.6%), mean diabetes duration 8.19 ± 6.96, and mean HbA1c 8.2 ± 2.1%. Prevalence of MA 40.81%, while the

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overt diabetic nephropathy was present in 2.8% of cases. 927 patients (33.3%) with newly diagnosed diabetes presented already MA. Central obesity, presence of hypertension >140/90 mmHg, HbA1c >8%, and diabetes duration >15 years were risk factors for microalbuminuria.

Conclusions
Diabetic nephropathy is a common chronic complication of diabetes mellitus. Its early detection, and an aggressive treatment of its risk factors may prevent its progression. The search for the presence of MA might be part of the initial assessment for each person with type 2 diabetes.

EP475
Glycaemic control and weight evolution in type 2 diabetic patients with dapagliflozin in addition to their previous treatment
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Introduction
From November 2013 it is available in Spain a new drug to treat type 2 diabetes (DM2): dapagliflozin. The new mechanism of action consists in the inhibition of the sodium–glucose co transporters (SLGT2) inhibiting glucose reabsorption in the proximal tubule and increasing glucose excreted in the urine. Therefore hyperglycaemia decreases and so does weight as a consequence of glycosuria. This is a very convenient side effect since DM2 is highly associated with overweight/obesity.

Methodology
This is an observational retrospective study where the results of ten patients (eight females and two males) after 3 months of treatment are shown.

Results
The average age was 58.2 (±10.5) years, nine patients had been diagnosed of obesity, average BMI was 37.1 (±8.6). The initial average HbA1c was 8.43% (±1.62) and the average weight was 94.5 (±20.9) kg, after 3 months of treatment. The average HbA1c was 7.45 (±0.86) and average weight 90.4 (±19.2) kg with a medium loss of 4.26 (0.2–14.5) kg. The uric acid levels were evaluated in eight patients. The initial average level was 5.63 (±1.46) mg/dl, and after 3 months of treatment it was 4.68 (±1.15) mg/dl. In the follow-up visit 90% of the patients were still on dapagliflozin. Three of them had a case of urinary infection, one decided to stop using the drug by herself, the other two patients were given antibiotic therapy and there was no need to stop using the drug.

No other side effects were described.

Conclusions
Dapagliflozin improved the glycaemic control; all the patients experienced a loss of weight; a decrease of the uric acid serum levels was seen; the most common side effect was non-complicated urinary infection that was solved with antibiotic therapy.

EP476
Pregnancy planning in type 1 diabetes mellitus
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Objective
The aim of this study was to determine the prevalence of pregnancy planning in women with type 1 diabetes mellitus (DM1) and analysing differences associated with unplanned pregnancy.

Patients and methods
Retrospective descriptive study of pregnancies in women with DM1 (2004–2012). Variables analysed: age, time of diabetes evolution, microvascular complications, and maternal outcomes (HbA1c, preeclampsia, abortions, and Caesarean section) and neonatal outcomes (perinatal death, gestational age at delivery, birth weight, and congenital malformations). The pregnancies were divided in groups attending to pregnancy planning and were analysed to evaluate possible differences between them (group 1: planned and group 2: unplanned).

Statistical analysis
Comparing proportions with the χ² and comparing means with Student’s t-test.

Results
132 pregnancies. Caucasian 99.2%. Unplanned pregnancy: 67.4%. Group 1 vs group 2: 31.84 ± 4 years old vs 29 ± 4.5 years old, P = 0.34; time of diabetes evolution: 13.5 ± 8.1 years vs 13.1 ± 7.7 years, P = 0.56; non-proliferative diabetic retinopathy: 4.6% vs 5.6%, P = 0.5; proliferative diabetic retinopathy 9.3% vs 8.9%, P = 0.9; microalbuminuria 0% vs 3.3%, P = 0.22; nephropathy 0% vs 2.24%, P = 0.32; hypertension 0% vs 2.24%, P = 0.32; undetected hypothyroidism: 23% vs 18.2%, P = 0.45; smoking 7% vs 12.5%, P = 0.33; HbA1c (%): before pregnancy 6.4 ± 0.4 vs 8.04 ± 1.3, P = 0.00; first trimester 6.36 ± 0.5 vs 7.6 ± 1, P = 0.004; second trimester 6.01 ± 0.5 vs 6.61 ± 1, P = 0.01; and third trimester 6.14 ± 0.77 vs 6.77 ± 0.7, P = 0.21. Maternal and neonatal outcomes (group 1 vs group 2): preeclampsia 0% vs 3.5%, P = 0.21; abortions 6.9% vs 8.04%, P = 0.7; Caesarean section 55% vs 44.8%, P = 0.3; perinatal death 0% vs 1.1%, P = 0.9; gestational age at delivery 38.5 ± 1.8 weeks vs 37.8 ± 2.4 weeks, P = 0.1; macrosomia 25.6% vs 35%, P = 0.28; neonatal hypoglycaemia 5% vs 3.3%, P = 0.9; and congenital malformations 7.2% vs 7.3%, P = 0.9.

Conclusions
Gestation planning is deficient and is associated with glycaemic control deficit at the beginning of gestation. Glycaemic control is similar in third trimester of pregnancy, and maternal and neonatal outcomes were similar in both groups.

EP477
Web-based telmedicine system is useful for monitoring glucose control in pregnancy women with diabetes
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Objective
The aim of this study was to examine the impact of a web-based telmedicine system for monitoring glucose control in pregnant women with diabetes on health care visits, metabolic control and pregnancy outcomes.

Subjects and methods
A prospective, single-centre, and interventional study with two parallel groups was performed in Puerto Real University Hospital (Spain). Women were assigned to two different glucose monitoring groups: control group (CG) that was managed only by follow-up with the Gestational Diabetes Unit (GDU) and telmedicine group (TMG) that was monitored both by more spaced GDU visits and a web-based telmedicine system. The number of health care visits, degree of metabolic control and maternal and neonatal outcomes were evaluated.

Results
104 pregnant women with diabetes (77 with gestational diabetes, 16 with type 1 diabetes, and 11 with type 2 diabetes) were included in the TMG (n = 40) or in the CG (n = 64). There were no significant differences in mean HbA1c level during pregnancy or after delivery, despite significantly lower number of visits to the GDU (3.2 ± 2.3 vs 5.9 ± 2.3 visits, P < 0.001), nurse educator (1.7 ± 1.3 vs 3.0 ± 1.7 visits, P < 0.001), and general practitioner (3.7 ± 2.0 vs 4.9 ± 2.8 visits, P < 0.034) in the TMG. There were no significant differences between groups in maternal or neonatal outcomes.

Conclusions
Web-based telmedicine system can be a useful tool facilitating the management of pregnant diabetic patients, as a complement to conventional follow up and could contribute to reduce the outpatient clinic visits.

EP478
Changes in diabetes related quality of life and clinical outcomes in patients with type 2 diabetes, after initiation of injectable treatment
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17th European Congress of Endocrinology 2015
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In this study, we enrolled 123 patients with DM2 that accordingly to the based on evidence clinical judgment, needed injectable treatment for the achievement of good glycaemic control. There was not significant changes at the whole sample in anthropometrics, but there was increase in insulin treated subgroup and decrease in GLP1 treated subgroup. Glycaemic control was improved ($P<0.001$), without differences between detemir vs glargine subgroups, but with more improvement of HbA1c in insulin treated vs GLP1 treated subgroup ($P<0.05$). Lipid parameters (TC, TG, LDL, and HDL) were improved ($P<0.001$), without changes between the subgroups, except the more significant reduction at TC in insulin treated vs GLP1 treated. No changes were detected at kidney function, neither at the SPP, but there was a reduction at the DPP ($P<0.05$). Hypoglycaemic episodes were increased after injectable treatment at the whole sample, and in the different subgroups, as GLP1 treated patients had less serious hypoglycaemic crisis. There was an improvement at the present quality of life (overview item I), no changes at the quality of life without diabetes (overview item II) and deterioration at the average weighted impact score of the 19 diabetes specific items of ADDQol-19, after commencement of injectable treatment.

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EP479

Does a nurse-led Diabetic Renal Clinic improve outcomes?
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Aim
To audit outcomes and adherence to prescription recommendations in a nurse-led Diabetic Renal Clinic.

Method
Baseline data at time of referral to the clinic was compared to the final clinic visit within a 12-month period (T1) of the first visit (T0), using information from clinical letters and electronic records of patients attending the clinic in our hospital within a 12-month period (T1) of the first visit (T0), using information from clinical letters and electronic records of patients attending the clinic in our hospital between 2010 and 2014. Patients without at least one follow-up data within a 12-month period were excluded.

Results
We had complete data in 91/208 patients seen. Average age was 63 years and 54 were males. A mean reduction of HbA1c from 74 to 69 mmol/mol ($P=0.01$) was achieved. Systolic blood pressure reduced from 152 to 142 mmHg ($P<0.01$), although no significant change in diastolic blood pressure was seen (75–73, $P=0.115$). Significant urinary albumin/creatinine ratio ($ACR$) improvement was observed – 53 down to 31 mg/mmol ($P<0.01$). Renal function declined from eGFR 54 to 51 ml/min per 1.73 m$^2$ ($P=0.001$). There was no significant difference in total cholesterol (4.4–4.3, $P=0.371$). 50 patients (54%) were not on an antplatelet agent at T1. All of these patients had at least one risk factor (age 50 years or above, systolic BP above 145 or microalbuminuria) and thus aspirin would have been indicated. Six of 17 (35%) patients not on a statin were prescribed one by T1. 79 (86%) were on a lipid-lowering agent at T1. 85% received an ACE inhibitor, ARB, or both.

Conclusion
These results from 1 year follow-up suggests that the nurse-led clinic is effective in reducing HbA1c, systolic blood pressure, and urine ACR levels in this high CV risk patients. This should hopefully result in improved cardiovascular and renal outcomes and appropriate referrals to renal specialist clinic. Most patients received lipid-lowering agents and ACE inhibitors/ARBs, whilst aspirin prescription remained low.

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EP480

Effect of liraglutide 1.8 mg in patients with non-controlled type 2 diabetes mellitus at an Endocrinology Clinic: LIED-2 study
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Background and aims
To describe the characteristics of patients with non-controlled type 2 diabetes mellitus with liraglutide treatment.

Materials and methods
Retrospective descriptive study, 85 outpatients (women 49, ages 18–86 years old with non-controlled type 2 diabetes mellitus) were evaluated between July 2013 and March 2014 and received treatment with liraglutide 1.8 mg SQ/day (0.6 mg SQ during the first week, 1.2 mg SQ during the second week, and 1.8 mg during the third week and the rest of the treatment). Age, sex, diagnosis time, weight, HbA1c, fasting glucose, systolic and diastolic blood pressure, pharmacological treatment during 6 months were extracted for analysis.

Results
Patients treated with liraglutide 1.8 mg as monotherapy or in conjunction with a therapeutic scheme decreased HbA1c values at 3 and 6 months (1.02%, 95% CI ±0.93, $P<0.0001$ and 2.08%, 95% CI ±0.8, $P<0.0001$); fasting glucose at 3 and 6 months (37 mg/dl, 95% CI ±33, $P<0.0001$ and 68 mg/dl, 95% CI ±26, $P<0.0001$); weight at 3 and 6 months (3 kg, 95% CI ±10, $P<0.0001$ and 5 kg, 95% CI ±10, $P<0.0001$); SBP at 3 and 6 months (9 mmHg, 95% CI ±15, $P<0.0001$ and 16 mmHg, 95% CI ±16, $P<0.0001$); and DBP at 3 and 6 months (3 mmHg, 95% CI ±6, $P<0.0001$ and 6 mmHg, 95% CI ±6, $P<0.0002$). 40% of patients reached HbA1c <7.0; 20% reduction of HbA1c, 39% reduction in fasting blood glucose, 6% reduction in mean weight (1–18%, 1–12 kg), 95% reached SBP <140 mmHg; 100% reached DBP <90 mmHg. Reported adverse events during treatment were nausea (27%), abdominal pain (18%), hypoglycaemia (14%), diarrhoea (9%), and respiratory symptoms (7%). Metformin was present in 65% cases of nausea, 55% cases of diarrhoea, and 43% of cases of abdominal pain. No fatal adverse events occurred.

Conclusion
Patients treated with liraglutide 1.8 mg SQ per day in monotherapy or in conjunction with a therapeutic scheme showed a decrease in HbA1c, fasting glucose, weight, SBP, and DBP during a 6-month treatment.

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EP481

Initial experience of SGLT2 inhibitor use in type 2 diabetes
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Introduction
SGLT2 inhibitors offer a novel approach to improve glycaemic control in patients with type 2 diabetes through inhibition of renal glucose reabsorption. Phase 3 clinical trials demonstrated consistent glucose lowering effects and weight loss. The objective of our audit was to assess the early effects of treatment with dapagliflozin 10 mg in our clinic population.

Methods
We performed a retrospective audit of clinical parameters in patients ($n=36$; mean age 55.2 years and diabetes mean duration 15.9 years) who attended our hospital in the previous year over a mean follow-up interval of 144 days (25–359 days). 13 patients were previously treated with dual oral agents and 15 with insulin (16–540 units).

Results
We observed a significant improvement in glycaemic control with an HbA1c fall from 85.6 to 72.9 mmol/mol ($P<0.01$). This was accompanied by a mean weight loss of 2.7 kg ($P<0.01$). There was a trend for BP reduction but this was non-significant. No significant correlations were observed between weight loss and other clinical variables. Non-responders were comparable to responders in terms of weight, age, and duration of diabetes. One patient discontinued therapy due to side effects (vulval candidiasis). Improvements in glycaemic control allowed for withdrawal of other agents in three patients including withdrawal of prandial insulin in one individual.

Conclusion
In conclusion, this audit of our early experience with the SGLT2 inhibitor dapagliflozin highlighted clinically meaningful improvements in parameters of glycaemic control, weight, and BMI. Long-term follow up for evidence of sustained drug efficacy in clinical practice is awaited.

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Fungal sinusitis caused by *Aspergillus* in a patient with type 1 diabetes

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Objective

Aspergillosis is defined as the infection of the *Aspergillus* type mould and is commonly seen in hemotologic malignacies, hematopoietic stem cell transplantation, aplastic anemia, primary immunodeficiency, and immunocompromised patients. Fungal sinusitis is poorly understood, and is generally presented as rhinonobicrocerebral involvement of mucormycosis. Herein, a fungal sinusitis caused by *Aspergillus* case presented with headache is reported. Case

Twenty-three-year-old male with a history of 9-year diabetes was admitted to our clinic because of high blood glucose level (with a HbA1c level of 14%) and headache which was lasting for 1 month without any pain relief. Cerebral computerized tomography was performed and hyper dens foci fulfilling left maxillary sinus was found. Fungal sinusitis was firstly thought. Tissue sampling from the foci was performed by Ear–Nose–Throat specialist by using endoscopic method. There was no reproduction of any organism in culture but *Aspergillus* structure was seen in biopsy sample. Bone destruction or orbital involvement was not seen according to radiological findings. Patient was diagnosed as fungal sinusitis. He was empirically treated with itraconazole. His tomography 3 months after the initiation of therapy and there was no sinusitis finding.

Discussion

Rhinoencephalic aspergillosis is commonly seen in neutropenic patients whereas mucormycosis is more frequent in diabetic patients. Aspergillosis is detected in a diabetic patient who did not have an additional risk factor. Fungus can colonize in upper and lower airways without causing infection. Only culture positivity is not enough for diagnosis. Invasive fungal sinusitis is diagnosed with the histopathologic evaluation of the biopsy material. Invasive fungal sinusitis is commonly seen in immunosuppressive patients and can cause life threatening conditions. In patients with uncontrolled diabetes and ketoacidosis, invasive fungal sinusitis can be seen.

Conclusion

Although, the most common cause of fungal sinusitis in diabetic patients is mucormycosis, *Aspergillus* must be kept in mind.

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Once-weekly exenatide in a real-world clinical setting: clinical outcomes and analysis of potential predictors of response

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Objective

The aim of this study is to evaluate the effectiveness of once-weekly exenatide on metabolic control, weight, blood pressure, and lipid profile in obese patients with type 2 diabetes (T2DM), and to assess possible predictive factors of response.

Material and methods

Retrospective observational study, conducted with adult obese (BMI ≥ 30 kg/m²) T2DM subjects that had been initiated once-weekly exenatide following routine clinical practice. Anthropometric measures, blood analysis, and blood pressure measures were collected at the initiation of once-weekly exenatide (V0) and after 16 ± 4 weeks of treatment (V1). Predictors of target metabolic response (HbA1c < 7%), were evaluated by using a multiple logistic model.

Results

31 patients were included (mean age 54.4 ± 10.7 years; female 54.8%; and mean duration of T2DM 7.9 ± 5.4 years). Significant changes from V0 to V1 were observed in weight-related parameters (body weight 108.1 ± 28.8 kg vs 101.3 ± 22.3 kg and BMI 41.2 ± 8 kg/m² vs 39.7 ± 7.3 kg/m², P < 0.001 for both); HbA1c (8.6 ± 1.6% vs 7.3 ± 1.3%, P < 0.001), lipid profile (total cholesterol 206.4 ± 37 mg/dl vs 181 ± 41.5 mg/dl, P = 0.002; LDL-cholesterol 124.3 ± 35.8 mg/dl vs 101.6 ± 39.2 mg/dl, P = 0.003; HDL-cholesterol 39.4 ± 10.7 vs 40.7 ± 10.3, P = 0.331; and triglycerides 238.1 ± 125.7 mg/dl vs 195.1 ± 80 mg/dl, P = 0.001). No differences in blood pressure (systolic or diastolic) or number of antihypertensive drugs were found. 45.2% of patients achieved HbA1c < 7%, 64.5% lost weight, and 41.9% simultaneously achieved HbA1c < 7% and lost weight. None of the studied variables (age, sex, duration of diabetes, baseline HbA1c, and BMI) were confirmed as predictors of response.

Conclusions

In obese patients with T2DM, once-weekly exenatide increases metabolic control, decreases body weight, and improves lipid profile. However, once-weekly exenatide does not exert beneficial effects on blood pressure. Age, sex, duration of diabetes, baseline HbA1c, and BMI were not predictors of efficacy of once-weekly exenatide.

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Association between peripheral vascular disease and other macrovascular and microvascular complications in diabetic patients

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Introduction

Diabetes mellitus is a condition on the increase, carrying a high risk of macro and microvascular disease. Previous studies suggest a link between microvascular and macrovascular complications in diabetes. However, just a few studies have investigated whether the presence of peripheral vascular disease (PVD) is associated with other macrovascular and microvascular complications in diabetes patients. So, this was the aim of our study.

Patients and methods

98 diabetic patients (68 with type 2 and 20 with type 1 diabetes) were included. PVD was confirmed by arteriography. Other macrovascular complications were collected, including: adverse cardiovascular events (myocardial infarction, angina, etc.) and stroke. Microvascular complications were, also, collected: retinopathy, nephropathy, and peripheral neuropathy.

Statistical analysis

χ² test was used to compare the existence of macro and microvascular complications between the groups with and without PVD.

Results

48 males and 50 females with mean age (52.58 ± 20.70) and mean HbA1c (11.21 ± 2.33%) were included. 14 patients (15.73%) were diagnosed of PVD. The existence of PVD was significantly correlated with the existence of more macrovascular complications (P < 0.001) and, at least, one microvascular complication (P < 0.005). Also, significant differences between the groups of patients with or without PVD were found in the rate of neuropathy (78.57 and 23.61%, respectively, P < 0.001); cardiovascular events (50.00 and 9.59%, respectively, P = 0.002) and in the rate of strokes (28.57 and 6.67%, respectively; P = 0.001). There were no significant differences in the rate of retinopathy and nephropathy between both groups.

Conclusions

Our results show significant correlation between the existence of PVD and the existence of more macrovascular complications and one or more microvascular complications. We have found that diabetic patients with PVD present significant higher rates of neuropathy, cardiovascular events and strokes. Despite the limitations of the study, our results suggest that diabetic patients with PVD require proper micro and macrovascular complications screening.

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Diabetic kidney disease and its association with macrovascular disease in diabetic patients

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Introduction

It is well known that diabetes confers a substantial burden of macrovascular disease. However, just a few studies have investigated the association between...
diabetic kidney disease (DKD) and cardiovascular disease. The purpose of this study is to investigate whether the presence of DKD is associated with macrovascular disease in diabetic patients. Patients and methods 98 diabetic patients (48 males/50 females) were included in the study. DKD was confirmed by the presence of moderately or severely increased albuminuria. Adverse cardiovascular events were collected, including: cardiac events, left ventricular hypertrophy (LVII), peripheral vascular disease (PVD), and stroke. Statistical analysis χ² test was used to compare the existence of macrovascular complications between groups with and without DKD.

Results 68 patients with type 2 diabetes and 20 with type 1, with mean age (52.58±20.70) and mean HbA1c (11.21±2.33%), were included in the study. DKD was diagnosed in 24 patients: 16 with moderately increased albuminuria and 8 with severely increased. DKD was significantly correlated with the existence of, at least, one macrovascular complication (P<0.02). Significant differences between the groups with or without DKD were found in the rate of cardiac events (32.00 and 9.84%, respectively; P=0.01); LVH (36.00 and 1.59%, respectively; P<0.001), and PVD (20.00 and 13.33%, respectively; P=0.04). These differences remained significant after adjusting for age, sex, hypertension, smoking habit, HbA1c, duration of diabetes, and BMI. No significant differences in the rate of strokes.

Conclusions Our results show significant correlation between DKD and the existence of one or more macrovascular complications. Moreover, we have found that diabetic patients with DKD present significant higher rates of cardiac events, LVH and PVD than diabetic patients without DKD. Despite the limitations of the study, our results suggest that early detection of DKD might be a valuable component of macrovascular risk assessment in diabetic patients.

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EP486 Intensive glycemic control fails to improve indices of vascular dysfunction in patients with type 2 diabetes; results at 6–12 months follow-up

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Background In subjects with long duration of type 2 diabetes (T2DM), strict glycemic control fails to decrease the incidence of cardiovascular disease (CVD). Impaired vascular indices have been associated with adverse cardiovascular prognosis in T2DM. We examined whether intensive glycemic control in T2DM patients improves vascular indices.

Methods We studied 68 T2DM patients (64±9 years, 52% males, and T2DM duration 14±10 years) with poor glycemic control (HbA1c >7.5%), at baseline and 6–12 months after intensive treatment to achieve optimal glycemic control. Brachial artery flow-mediated dilation (FMD), carotid-femoral pulse wave velocity (PWV), central augmentation index (AIx), large and small artery elasticity indices, common carotid intima–media thickness (cIMT), and ankle–brachial index were measured.

Results Improvement of HbA1c >0.5% was achieved in 55 (81%) patients (HbA1c decrease from 9.6±2.18 to 7.3±1.0%, P<0.001). In this group of patients, triglycerides decreased (177±140–137±73 mg/dl, P=0.008), cIMT increased (0.70±0.20–0.74±0.22 mm, P=0.038), and large artery distensibility decreased (14.2±5.2–12.4±4.1 AU, P=0.045) at follow-up, while no other changes in vascular indices, blood pressure, lipids, or other laboratory values were found. No difference in vascular indices’ changes at follow-up was observed between patients with or without improved glycemic control (repeated measures (RM)-ANOVA, P=NS for all). When patients with improved glycemic control were compared based on T2DM duration, AIx was decreased in those with short disease duration (<5 years), while it remained unchanged in those with >5 years duration (RM-ANOVA, P=0.013).

Conclusions In T2DM patients, aggressive glycemic control without concomitant improvement in other cardiovascular risk factors was not associated with an improvement in vascular function indices at 6–12 months. However, in patients of <5 years duration, intensive glycemic control improved only augmentation index, a combined index of aortic stiffness and peripheral vascular function. Multifactorial interventions of longer duration are needed to improve cardiovascular risk in T2DM.

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EP487 Intracocular pressure change during oral glucose tolerance test in non-diabetic individuals

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Introduction A significance of chronic hyperglycaemia related to the rising intraocular pressure are discussed in the previous studies. The purpose of the present study was to investigate changes of intraocular pressure induced by acute changes of glucose levels during oral glucose tolerance test in non-diabetic subjects.

Methods Fifty-one individuals who were needed to be screened for diabetes, were scheduled for oral glucose tolerance test according to the World Health Organization criteria. Biochemical parameters associated with metabolic syndrome, insulin resistance (HOMA-IR) and systolic and diastolic pressure were also measured. Complete ophthalmologic examination was performed before the test. The inclusion criteria were having a normal intraocular pressure (<21 mmHg), and having no eye disease, no ophthalmic surgery or no glaucomatous optic nerve appearance. During the test, intraocular pressure was measured by using rebound tonometry (ICARE) two times at the fasting state and at first and second hours after oral glucose administration.

Results The mean age of the patients was 46.24±11.31 years. The mean BMI was 29.63±5.25 kg/m². The median fasting glucose and intraocular pressure for right was 100 mg/dl (91.250–105.750) and 17 mmHg. The median glucose and intraocular pressure level for right eye in the first hour and in the second hour in OGTT were 153 mg/dl (123.5–190.5), 18 mmHg (14–22) and 171 mg/dl (92.25–140) and 18 mmHg (14–20.75) respectively. The intraocular pressure right eye were significantly higher in the first hour compared to the fasting values (P<0.05).

Conclusion The relation between diabetes mellitus and glaucoma has been addressed in many studies with no clear underlying mechanisms. In our study on healthy non-diabetic individuals, acute hyperglycaemia has found to have a positive relationship with intraocular pressure, suggesting that acute hyperglycaemia may represent a possible mechanism.

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EP488 Hypoglycaemia due to drug interaction with clarithromycin

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Introduction Interaction between diabetes mellitus (DM) and an infection usually results in hyperglycaemia. However, there is data describing hypoglycaemia events related with the association between certain antibiotics and oral anti-diabetic drugs or insulin.

Case report Male, 73 years old, with history of hypertension, obesity and dyslipidaemia. DM type 2 was diagnosed 13 years ago with any macro or microvascular complications so far. Currently he’s treated with insulin detemir (40 + 28U) and vildagliptin+metformin 50/1000 2id, maintaining good metabolic control (HbA1c 6.9%) with rare episodes of hypoglycaemia. Owing to dental abscess he started a treatment with clarithromycin 500 mg bid. After 36 h of taking the drug, referred two episodes of night symptomatic hypoglycaemia, on consecutive days (42 and 37 mg/dl respectively), which reversed after sugar intake. In this context, he went to our clinic, and the antibiotic was changed to amoxicillin + clavulanic 850 + 125 mg, keeping the usual therapy for DM. There weren’t any more episodes of hypoglycaemia.

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In the literature there are few reports of hypoglycaemia induced by clarithromycin in combination with insulin detemir. 40–70% of clarithromycin circulates bound to proteins, which can dissociate insulin detemir of protein binding sites (98% bonds to albumin), increasing the free concentration and its pharmacological effects. This phenomenon can cause a faster beginning of action, simulating an insulin with intermediate or short-action, leading to hypoglycaemia. Clarithromycin is a potent inhibitor of CYP3A4. Vildagliptin isn’t a substrate of this cytochrome. Metformin is a substrate of this cytochrome’s family, but there isn’t any report of hypoglycaemia with this association.

Clinicians should be aware of this drug interaction, regarding the need of adjustments of insulin doses to avoid possible adverse effects and hospitalizations. Patients who start clarithromycin should be advised to have more frequent monitoring capillary blood glucose and re-educated about the signs, symptoms, and treatment of hypoglycaemia.

Conclusions

In this retrospective study, we evaluated 673 diabetic patients, of whom 57.8% were males and 42.2% females. Mean patient age was 55.6 years and the mean duration of diabetes 81 ± 86.9 months.

Results

The mean level of HbA1c was 9.0 ± 2.4% (4.5–18); the mean serum creatinine level was 0.83 ± 0.22 mg/dL (0.3–1.5); and the mean Mg level 1.97 ± 0.25 (1.13–3.0) mg/dL. Total of 55 (8.2%) patients had diabetic retinopathy and 95 (14.1%) diabetic neuropathy. Of all patients, Five hundred patients 74.3% of patients had normoalbuminuria, 133 19.8% of microalbuminuria, and 40 5.9% of overt proteinuria. 171 patients (25.4%) had HbA1c levels equal or below 7%; and 502 patients (74.6%) had HbA1c levels above 7%. The patients were divided into two groups in terms of their serum Mg levels; low-level (≤ 1.8 µg/dl) and normal (1.9–2.6 µg/dl). No between-group difference in any of BMI, fat mass, total body water (TBW), fasting glucose (FG) level, lipid parameters, sodium or potassium levels, or glomerular filtration rate (GFR), was apparent. Although, the groups did not differ in terms of retinopathy or neuropathy levels, microalbuminuria was more common in hypomagnesemic patients (P = 0.004). HbA1c levels did not differ between the groups (P = 0.243). However, a weak negative correlation was apparent between serum Mg and HbA1c levels (r = −0.110, P = 0.004) and also between serum Mg level and overt proteinuria (r = −0.127, P = 0.018).

Conclusion

Mg depletion is a common problem in patients with diabetes mellitus. It affects both glycaemic regulation and emergency of complications. Serum Mg level affected both glycaemic regulation and the extent of emergency diabetic complications. Also, poor glycaemic regulation affected serum Mg levels.

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EP491
Scleredema in a patient with long-standing type 2 diabetes mellitus

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Introduction

Scleredema is a rare skin disease, clinically presents as diffuse, painless induration, and thickening of skin. It primarily affects the upper part of body and usually occurs in association with diabetes mellitus, infections or mononuclear gammopathy. We discussed a case of scleredema in patient with history of diabetes mellitus.

Case report

A 54-year-old woman with history of long-standing, poorly-controlled diabetes mellitus, hypertension, and coronary artery disease was referred to our department. She complained to gradually-developing several months, and hardening erythematous plaques on the neck and upper back. Her medication included metformin (2000 mg/day) and premixed insulin (50 U/day). Physical examination revealed edematous, erythematous plaques on posterior neck and upper back. Other systemic evaluations were normal. Complete blood count and comprehensive biochemical panel were normal, except of fasting blood glucose of 277 mg/dl. HbA1c was 11.8%. The patient was examined by dermatologist and skin biopsy was performed. On histopathological examination; epidermis was normal but there is prominent separation of collagen fibres throughout the dermis, thickening of the dermis and coarsening of collagen. Focal alcin blue positive mucine was also detected. Histopathological findings were consistent with scleredema. She had shown no infection so far. Scleredema was thought to be secondary to diabetes. She was started on intensive insulin regimen and glucose levels decreased within normal range. She was started on local PUVA therapy. After 2 months; redness and oedema of skin has partially disappeared, mobility of the back improved and skin of upper back was softer.

Conclusion

Scleredema diabeticorum is a rare complication of diabetes and reveals in obese subjects with long standing and poorly controlled diabetes mellitus. It can be clinically and histopathologically differentiated by other fibrosing disorders.
Coated pellets with controlled glucose release for interdiction of hypoglycaemia in children with diabetes

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Introduction
A diet plan, meals with suitable glycaemic index and sophisticated insulin delivery are used for balanced saccharides–insulin intake. In specific real day-to-day life situations patients must break their activities. Urgency to eat in socially inappropriate time harm their lives, especially in young children with diabetes. Night hypoglycaemia, a parental fear of insufficient snack in nursery, sports with prolonged race periods, etc. are among these situations. Controlled glucose release formulation with 2, 4, and 6 h lag time offers chance to substitute snacks or other meals in advance, allowing to decrease life inconvenience and improve therapy adherence of children with diabetes and their parents.

Design
A dosage form with controlled glucose release was prepared, a release period of 2–4 h was achieved. Optimal diameter, resistance of the coat, volume, taste, and acceptable form to swallow were refined in pharmaceutical treat.

Results
An amount of two exchange units is easy to add to standard meals, e.g. yoghurt. Pellets (clinically powder) do not cause abdominal discomfort. In CGM studies, formulation prevent night hypoglycaemia.

Conclusions
The formulation with controlled glucose release with specific easy-to-explain lag time offers additional means for diabetes treatment.

Coated pellets with controlled glucose release for interdiction of hypoglycaemia in children with diabetes

EP493

Different glycaemic patterns in patients with steroid diabetes and type 2 diabetes

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Introduction
Long-term use of glucocorticoids has impact on reduction of β-cell function and peripheral insulin sensitivity, leading to a steroid diabetes.

Aim
To assess patterns of change of glycaemia and need for insulin at admission to hospital, during days 1–5 and at discharge in patients with newly diagnosed type 2 diabetes (NST) compared with patients with a history of taking corticosteroids and newly diagnosed diabetes mellitus (ST).

Material and methods
Twenty patients with newly diagnosed diabetes were included; ten without, and ten with a history of taking corticosteroids. The day after admission (day 1) basal-bolus insulin scheme was introduced. Bolus insulin was used in the initial dose of 0.05 U/kg per meal, and a basal insulin (NPH) 0.2 U/kg BW at bedtime. The changes of glycaemia during 1–5 days were observed by measurement of plasma glucose profile before meals and 2 h after/before bedtime, and the need for insulin during the investigated time was recorded. A statistical analysis of data was performed.

Results
12 women (six NST and six ST) and eight men (four NST and four ST) were included in the study. The longest period of taking corticosteroids was 150 days, with a cumulative dose of 9600 mg of methylprednisolone. Statistically significant differences (P < 0.05) were observed: in total dose bolus insulin and the number of units per kilogram BW before dinner between NST and ST groups, and in the ST group in the first 5 days of treatment vs. at discharge; changes in plasma glucose in the period after lunch to dinner in ST group. There was a positive correlation between the cumulative dose of corticosteroids and the plasma glucose at admission at women in ST group.

Conclusion
Corticosteroids primarily cause hyperglycaemia in the afternoon and evening, and the targeted treatment and monitoring of glycaemic control should be directed to the above hours.

EP494

Angiopoietin 1 in patients with type 2 diabetes mellitus and diabetic retinopathy

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Background
Diabetic retinopathy (DR) is a clinically well-defined sight-threatening complication in type 2 diabetes. Angiopoietin 1 (Ang1) has been shown to promote endothelial cell survival without causing proliferation, stabilise endothelial interactions with surrounding support cells and can block the vascular permeability effects of vascular endothelial growth factor (VEGF). More recent data suggest that balance between these growth factors may affect vascular endothelial integrity and may be involved in the pathogenesis of diabetic retinopathy.

Aim of the study
To evaluate serum level of Ang1 in patients with DR and its relation to the severity of DR.

Methods
This is a cross sectional study comprised 75 patients with type 2 diabetes mellitus. They were divided into four groups, group A: 25 diabetic patients with proliferative DR (PDR), group B: 25 diabetic patients with non-proliferative DR (NPDR), group C: 25 diabetic patients with normal fundus, and group D: 50 healthy volunteers of matched age and sex.

Results
There was a high statistically significant reduction in serum level of Ang1 in diabetic patients (622.53 ± 394.94) than the healthy control group (1637.00 ± 253.50), P < 0.001. Ang1 was significantly lower among group A (PDR) (336.83) than the healthy control group (1637.00) and group B (NPDR) (489.60 ± 226.89), and group C (1047.20 ± 336.83). Correlation between Ang1 vs the other variables showed a highly significant negative correlation between Ang1 and HbA1c (P < 0.001) and a significant negative correlation with albumin/creatinine ratio (ACR), P < 0.02. Conclusion
There is a significant reduction in serum Ang1 in patients with DR and correlated with the severity of DR. This reduction of Ang1 may reflect in the role in the pathogenesis and progression of DR.

EP495

Eighteen grams of glucose are necessary to treat severe hypoglycaemia: experience from the Emergency Medical Services Department

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We know that non-severe hypoglycaemia (SH) should be treated with the immediate intake of 15–20 g of oral glucose, there are no data according to our knowledge in the current literature for the dose of glucose that is necessary to inject in SH. We have analysed retrospectively the treatment of pre hospital SHs as reported after an emergency call for intervention. Our primary objective was to know the dose of the given glucose and our secondary objective was to know the factors involved in determining these doses. Between April 2012 and December 2013 148 cases with SH were analysed retrospectively. A total of 104 cases (77 patients) were included in the final analysis, there were 29 women, patients had a mean age of 62 ± 19 years and 62/77 were on insulin therapy. The kidney function, the insulin dose and the duration of symptoms on arrival was unknown in most cases. Almost half of the patients (49.5%) were admitted in the nearby hospital after the intervention Patients that were not admitted had a pasta meal. Average blood glucose on arrival was 29 and 121 mg/dL at the departure of the emergency team. The average dose of injected glucose was 18 g (range 6–69 g)
EP496
SUMO4 163G>A variation is associated with kidney disease in type 2 diabetes in Indian population
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Background
Various genetic and environmental factors are appear to contribute to the development of kidney disease in type 2 diabetes. Small ubiquitin-related modifier 4 (SUMO4) appear to play a role in development and/or progression of diabetic nephropathy. Substitution of methionine with valine at codon 55 (M55V) of SUMO4 enhances activity of nuclear factor-kB, a central mediator of inflammation proapoptotic events.

Aims
To investigate the association between the SUMO4 M55V (rs237025, 163G>A) variant and kidney disease in north Indian individuals with type 2 diabetes.

Materials and methods
A case-control analysis was performed using genomic DNA samples from 201 subjects with diabetic nephropathy (DN) and 216 patients with diabetes but no kidney disease (DM). The SUMO4 163G>A polymorphic region was amplified using PCR and genotyping was done by digestion of amplified PCR product with restriction enzyme Msel.

Results
The duration of diabetes was higher in DN compared to DM (P=0.001). Clinical characteristics like blood pressure, cholesterol, triglycerides, HbA1c, and serum creatinine were significantly different between the two groups (P<0.001). The frequency of other diabetic complication like neuropathy and retinopathy was also significantly greater in DN (P<0.001). The genotypic and allelic frequencies of the studies variant were significantly different in DM and DN groups. GG genotype and G allele were significantly more frequent in DN as compared to DM ((GG: P = 0.018, OR = 1.72, 95% CI 1.1–2.7) (G: P = 0.017, OR = 1.4, 95% CI 1.1–1.8)).

Conclusions
This study shows that SUMO4 163G>A polymorphism might be associated with susceptibility to diabetic nephropathy.

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EP497
Feasibility, acceptability, and uptake rates of gestational diabetes mellitus screening in primary care vs secondary care: findings from a randomised controlled mixed methods trial
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Introduction
It is postulated that uptake rates for gestational diabetes mellitus (GDM) screening would be improved if offered in a setting more accessible to the patient. However, this has not been previously investigated, nor has the feasibility or the acceptability of such an alternative. The aim of this study is to evaluate the rate of uptake of GDM screening in the primary vs secondary care setting, and to qualitatively explore the providers’ experience of primary care screening provision.

Methods
This mixed methods study was composed of a quantitative unblinded parallel group randomised controlled trial and qualitative interview trial. 781 pregnant women were randomised to receive a 2-h, 75 g oral glucose tolerance test in either the primary (n=391) or secondary care (n=390) setting. Semi-structured interviews with 13 primary care providers were conducted.

Results
Statistically significant differences were noted between the two quantitative study arms for uptake rates (52.7% in primary care compared to 89.2% in secondary care; P<0.001), crossover rates (32.5% in primary care compared to 2.3% in secondary care; P<0.001), and non-uptake rates (14.8% in primary care compared to 8.5% in secondary care; P=0.005). Of the total potential participants, 37.2% (n=1206) could not be involved as their primary care provider did not engage with the trial. Primary care providers reported difficulties with the conductance of GDM screening citing workload, logistical challenges and lack of remuneration as problematic, while recognising primary care as the most appropriate and preferable location for screening.

Conclusions
Currently, provision of GDM screening in primary care in Ireland, despite its acknowledged benefits, is unfeasible due to poor uptake rates, poor rates of primary care provider engagement and primary care provider concerns, particularly with regard to resourcing limitations.

Disclosure
This work was supported by the Health Research Board of Ireland (grant number ICE/2011/3).

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EP498
Real-time sonoelastography and ultrasound evaluation of Achilles tendon of diabetic patients
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Introduction
Diabetes mellitus (DM) is an endocrine disease characterised by metabolic abnormalities and long-term complications. Achilles tendon (AT) play an important role in foot biomechanics. We aimed to investigate the effect of DM on the AT, which may contribute to the long-term complications in the foot–ankle complex.

Materials and methods
78 diabetic patients with (35 cases) or without (43 cases) diabetic foot ulcers were recruited from Endocrinology Clinic. Thirty-three age, gender, and BMI matched non-diabetic healthy individuals with no history of Achilles tendinopathy were selected among hospital staff as controls. All participants underwent ultrasonography and sonoelastography of their ATs for evaluating AT thickness (ATT) and stiffness (ATS). Each patient was also tested for fasting plasma glucose (FPG) and HbA1c as a measure of diabetes control. Other chronic complications were also evaluated in all diabetic patients.

Results
The AT was significantly thicker in the diabetic patients with diabetic foot ulcers compared to diabetics without any ulcer and the controls (P<0.001). The ATT correlated with the BMI (r=0.224, P=0.04) and age (r=0.419, P=0.001). HbA1c, FPG, and duration of diabetes were higher for diabetic patients with foot ulcers. We observed that the ATT values were positively correlated with neuropathy (P=0.001), retinopathy (P=0.001), nephropathy (P=0.006), peripheral arterial disease (P=0.001), and coronary arterial disease (P=0.005) in diabetic patients without foot ulcers. But this correlation wasn’t detected for diabetic patients with foot ulcers. ATS decreased in the diabetic patients with diabetic foot ulcers.

Conclusion
Diabetic patients with diabetic foot ulcers have softer and thicker AT then the other diabetics and healthy controls. This is the first study reported that research sonoelastography of AT of diabetic patients.

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EP499
Effect of gemigliptin switching from pioglitazone with metformin in type 2 diabetes
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The DP4 inhibitors that increase insulin secretion by glucose dependently can also relieve insulin resistance because they improve early phase insulin secretion and prevent late hyperinsulinemia. It also can be more effective in controlling the blood glucose because it acts synergistically with metformin by improving insulin secretory dysfunction compared T2DM with metformin that has similar action mechanism. One of those is gemglitpic that was developed in this country recently and there are not many clinical studies. So, we observed the effect of gemgilipitin with metformin compared to pioglitazone with metformin. We recruited 81 type 2 DM who failed in glucose control target below 7% of HbA1c or have side effect such as weight gain with metformin plus pioglitazone. The 15 mg of pioglitazone was used when it was switched because the usual dose permitted by national insurance was 15 mg at that time. Pioglitazone was switched to gemgilipitin without changing the dose of metformin. The mean HbA1c level of 3 months and just before switching was compared to the mean of 3 and 6 months after switching. The difference of weight and HOMA-IR just before and 6 months after switching was also compared. The age was 56.4 ± 10.0 and mean BMI was 26.3 ± 5.4. The mean HbA1c level before switching was 7.1 ± 4.46. The HbA1c level was decreased in 72 patients (89%). The mean decrement of HbA1c was 0.58 ± 0.39 in above group. The body weight was increased (1.2 ± 0.39 kg) in 27 (33%) and decreased (2.9 ± 2.58 kg) in 48 (59%). The mean BMI was lower in weight gain group (24.1 ± 9.7) than in weight loss group (29.0 ± 5.5). The mean HOMA-IR before switching was 2.54 ± 2.55. HOMA-IR was increased in 67% and mean was 1.51 ± 1.47. It was decreased in 33% and mean was 0.43 ± 0.16. The gemgilipitin can be a good substitute to improve glucose control when failed with 15 mg of pioglitazone with metformin. It is more effective in weight control especially in high BMI group.

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EP500

Cytokine status and subpopulations of peripheral blood lymphocytes in patients with type 2 diabetes mellitus and non-alcoholic fatty liver disease

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One of the leading roles in the mechanisms of type 2 diabetes mellitus (T2DM) belongs to immunopathological link of pathogenesis, which determines the development rate and severity of its specific complications, in particular, non-alcoholic fatty liver disease (NAFLD).

The purpose

To examine the contents of cytokines and major lymphocyte subsets in patients with T2DM and NAFLD.

Description of methods

We observed 118 patients, including 64 patients with T2DM and NAFLD, 26 patients with T2DM and 28 patients with NAFLD. The control group consisted of 25 apparently healthy individuals.

Results

Identified changes in the level of cytokines and lymphocyte subpopulation composition in combination of T2DM with NAFLD can be used both for diagnosis and for predicting adverse development of this disease, in particular the development of the inflammatory response in the liver (increased level of IL1β), intensity and orientation of immunopathological reactions (increased IFNγ level, decreased IL4 level, and changed NK cells level), the intensity of proliferation of connective tissue and fibrosis formation (increased IL10 level).

Conclusions

In patients with T2DM, NAFLD or a combination of these abnormalities are observed changes in cytokine status, reflecting the intensity of the inflammatory immune responses, their direction and possible forecast of liver fibrosis. Increased blood levels of IL1β, IL17, and IFNγ indicate the presence of high inflammatory and immunopathological reactions in patients with T2DM and NAFLD. Imbalance is observed in the composition of lymphocyte subpopulations, manifested by decrees of CD8+ and CD16+ lymphocytes at a relatively stable level of T helper (CD4+) lymphocytes and increased content of CD20+ lymphocytes which develops against the background of increased level of circulating immune complexes. In patients with NAFLD and T2DM increased apoptotic preparedness of lymphocytes were revealed, which manifests as increased content of CD95+ cells in the blood.

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EP501

Evaluation of violation vibration sensitivity for early diagnosis of diabetic distal polyneuropathy in patients with type 1 diabetes in the Republic of Belarus

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Screening for diabetic polyneuropathy (DP) is advisable for all patients with type 1 diabetes mellitus (T1DM) after 5 years the detection of the disease. The aim of the study was to evaluate the vibration sensitivity disorders in T1DM patients using Vibratip device for early diagnosis of DP.

Materials and methods

509 patients with T1DM (224 women and 285 men) (mean age: 28.5 ± 8.5 years, mean BMI – 24.2 ± 4.1 kg/m2) were examined. The research was conducted within the framework of the republican action ‘optimization of approaches to improve the early diagnosis and prevention of diabetic polyneuropathy’. According to the criteria for inclusion in the research were examined patients with T1DM duration of disease is not more than 5 years (duration of DM: 3.3 ± 1.6 years). During the campaign was carried out a survey in individuals who seek health care institutions of the Republic of Belarus, the analysis of the medical documentation and examination of patients with an estimate of the sensitivity stop using the device Vibratip.

Results

The most common clinical symptoms of DP were: pain – 69 (13.6%) patients, burning – 83 (16.3%), numbness – 134 (26.3%), feeling of pins and needles – 152 (29.9%), and feeling of electric shock – 25 (4.9%) in patients with T1DM. Sensory disturbances feet were found in 23.6% (120) of diabetic patients: 12.6% (64) women and 11% (56) males using Vibratip device.

Conclusions

The data confirmed the high incidence of violation of vibration sensitivity in patients with T1DM with disease duration of <5 years.

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EP502

Disabilities of the arm, shoulder, and hand (DASH) questionnaire and diabetic complications: preliminary results

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Aim

Disabilities of the arm, shoulder, and hand (DASH) questionnaire is a self-administered region-specific outcome instrument developed as a measure of self-rated upper-extremity disability symptoms. DASH consists mainly of 30-item disability/symptom scale. In this study, we aimed to evaluate DASH questionnaire in 1000 type 2 diabetes mellitus (T2DM) patients.

Material and methods

297 patients (mean age 52.13 ± 9.37 years, 190 women and 107 men) who had T2DM were included as a preliminary in this study. The presence of cheiroarthropathy, Dupuytren’s contracture, tendon sign, and tendinitis was assessed. Diabetic retinopathy was assessed by direct ophthalmoscopy. Urinary albumin excretion was determined in at least two 24-hr urine samples. DASH questionnaire was administered to the diabetic patients. Direct measurements of parameters were performed with a Tanita body composition analyser. The bioimpedance parameters we measured were body fat percentage (%BF), total body fat (TBF, kg), and BMI.

Results

The mean diabetic duration was 7.71 ± 6.28 years. Dupuytren’s contracture was present in 7.7%, cheiroarthropathy in 11.1%, tendon sign in 19.5%, and tendinitis in 4.4%. Retinopathy was present in 15.5%, nephropathy in 18.2%. DASH score was 68.00 ± 31.70. Mean BMI was 32.28 ± 5.80. Mean TBF was 29.22 ± 11.77 kg. Mean %BF was 34.00 ± 10.19. There was positive correlation between DASH score and cheiroarthropathy, tendon sign, and tendinitis (P = 0.006, r = 0.159; P = 0.000, r = 0.214; and P = 0.004, r = 0.168 respectively). There was positive correlation between DASH score and BMI and TBF and %BF (P = 0.000, r = 288;
Topical wound pressurised oxygen therapy: new approach in treatment of diabetic foot ulcers?

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Introduction
Topical wound oxygen therapy (TWO2) is therapeutic modality that delivers humidified pressurised O₂ directly to the specific body part to achieve tissue penetration and increased O₂ levels to the open ischaemia wound. O₂ is vital in the synthesis of collagen, enhancement of fibroblasts, angiogenesis, leukocyte function, energy metabolism, and the inhibition of mycrobial growth. TWO2 therapy has showed effectiveness as an adjunctive therapy for the management of acute and chronic diabetic foot ulcers, venous stasis ulcers, pressure ulcers, and mixed ulcers.

Materials and methods
Five male patients aged 50–77 years with chronic diabetic foot ulcers grade 2A or worse according to the University of Texas wound Classification system (UTI) and ankle–brachial index (ABI) at least 0.5 in the affected limb were treated with TWO2 60 min daily, Monday through Friday for 6 weeks. Wound size measuring, microbiological samples, and digital photography of the wound were done once weekly. Wounds were debrided prior to therapy by the vascular surgeon, who assessed the wound every 7–10 days and debrided it if necessary. If infection was present antibiotics were given according to the antibioticogram.

Results
Wound area reduced from average 8.86–2.54 cm². Ulcer classification changed from UTI 2-B, 2-C and 2-D to 1-A and 0-A. Infection was absent in all wounds comparing to four infected wounds at the beginning.

Conclusion
Although current studies have shown effectiveness of TWO2 in treatment of diabetic foot ulcers, there are no specific cost effectiveness studies completed and there have been no studies found that show improved quality of life for patients receiving TWO2. The most important thing is that there are no standardised protocols for TWO2. So, randomised control studies are needed to increase the evidence around the use and effectiveness of TWO2 therapy and to establish optimal parameters for use.

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Relation between psychiatric symptoms and diabetic complications: preliminary results

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Aim
In this study, we aimed to assess psychiatric symptoms in 1000 type 2 diabetes mellitus (T2DM) patients.

Material and methods
297 patients (mean age 52.13 ± 9.37 years, 190 women and 107 men) who had T2DM were included as a preliminary in this study. The presence of cheiroarthropathy, Dupuytren’s contracture, tinnel sign, and tendinitis was assessed. Diabetic retinopathy was assessed by direct ophthalmoscopy. Urinary albumin excretion was determined in at least two 24 h urine samples. Beck’s Depression Inventory (BDI) and Beck’s Anxiety Inventory (BAI) were administered.

Results
The mean diabetic duration was 7.71 ± 6.28 years. Dupuytren’s contracture was present in 7.7%, cheiroarthropathy in 11.1%, tinnel sign in 19.5%, and tendinitis in 4.4%. Retinopathy was present in 15.5%, nephropathy in 18.2%. BDI score was 13.92 ± 9.93 and BAI score was 16.89 ± 13.63. There was positive correlation between BDI score and diabetic nephropathy (P = 0.001, r = 197). Also, there was positive correlation between BDI score and tinnel sign (P = 0.000, r = 241). Positive correlation between BAI score and diabetic retinopathy was detected (r = 0.019, r = 136). There was positive correlation between BAI score and tinnel sign (P = 0.00, r = 232). The suggested BDI cutoff of ≥ 17 had 81% sensitivity and 79% specificity and classified as clinically depressed. In our study BDI score ≥ 17 was 33.3%. BAI score ≥ 17 was classified as moderate and serious anxious. In our study BAI score ≥ 17 was 40.4%.

Conclusions
Psychiatric symptoms, especially depression and anxiety, are widely seen in patients with diabetes mellitus. Quality of life and disability are correlated with depression and anxiety levels. Therefore, in addition to the recent management of DM, psychiatric symptoms such as depressed mood and anxiety should also be taken into consideration in order to increase the quality of life in DM patients.

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The diabetic hand: a forgotten complication?

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Aim
Diabetes mellitus is a chronic metabolic condition characterised by persistent hyperglycaemia with resultant morbidity and mortality related primarily to its associated microvascular and macrovascular complications. In this study our aim was to investigate the prevalence of the most frequently occurring hand complications in 1000 type 2 diabetes mellitus (T2DM) patients.

Material and methods
297 patients (mean age 52.13 ± 9.37 years, 190 women and 107 men) who had T2DM were included as a preliminary in this study. The presence of cheiroarthropathy, Dupuytren’s contracture, tinnel sign, and tendinitis was assessed. All patients were evaluated also by the Rheumatology Division. Diabetic retinopathy was assessed by direct ophthalmoscopy. Urinary albumin excretion was determined in at least two 24 h urine samples.

Results
The mean diabetic duration was 7.71 ± 6.28 years. Dupuytren’s contracture was present in 7.7%, cheiroarthropathy in 11.1%, tinnel sign in 19.5%, and tendinitis in 4.4%. Retinopathy was present in 15.5% and nephropathy in 18.2%. Mean HbA1c was 8.58 ± 2.03. Mean fasting glucose was 174.6 ± 69.22 mg/dl. The relationship between these complications and patients’ age, sex, duration of diabetes, and glycemic control was also analysed. There was positive correlation between age and cheiroarthropathy and dupuytren’s contracture (P = 0.01, r = 193 and P = 0.000, r = 248 respectively). There was positive correlation between diabetic duration and diabetic retinopathy (P = 0.000, r = 216). There was positive correlation between diabetic duration and cheiroarthropathy (P = 0.044, r = 117). There was positive correlation between diabetic nephropathy and tinnel sign (P = 0.003, r = 164).

Conclusions
Some musculoskeletal disorders are more prevalent in T2DM patients and this may be associated with duration of diabetes. Also the hand abnormalities were associated with the diabetic complications. Long-term prospective randomised controlled trials on preventing musculoskeletal complications and disability in diabetics are needed.

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Moderate and severe hypoglycaemia associated metabolic changes in cortex and hippocampus of mice

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Objective
It is common in the clinical setting that the reperfusion of glucose after severe hypoglycaemia. Starvation leads to decrease in blood glucose level (BGL) and this shifts the brain to utilize less glucose and utilize other alternative fuels. This led us investigate how the brain decreases the glucose uptake during starvation and how it utilizes the glucose under severe hypoglycaemia.

Results
To understand the mechanism we checked the neuronal glut3, glut1 in expression by western blot analysis in the cortex and hippocampus in 24 h fasted and 2 IU/kg insulin induced hypoglycaemia mice at different intervals (10, 30, and 90 min). Our results suggesting that 24 h fasting significantly decreases the BGL (58 ± 2 mg/dl) from fed mice BGL (120.3 ± 6) and it slightly decreases the glut3 in cortex and hippocampus. In the insulin induced hypoglycaemia group, the BGL of 10 min after was (67.8 mg/dl), 30 min after was (54.80 mg/dl) and 90 min after was below (20 mg/dl). The glut3 expression in the 10 min in not altered but the 30 min after insulin administration decreases the glut3 more but not significant, whereas the glut3 in the 90 min after was restored to normal level. No change in the expression glut1 was observed.

Conclusion
The decreased BGL at the range nearly of 60 mg/dl during fasting or insulin induced hypoglycaemia, the neuron may utilize less glucose (decreased glut3) and may prefer astrocyte lactate (no change in glut1) and other fuel for metabolism. The decreased BGL below 20 mg/dl, the neuron may try to utilize the glucose directly (restored glut3) and from astrocytes (no change in glut1) and also from other fuels to restore the normal metabolism.

Disclosure
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Diabetes mellitus and chronic kidney disease: two decades of consultation of diabetes and kidney transplant, a retrospective study

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Aim
At 24th European Congress of Endocrinology 2015 Portugal

17th European Congress of Endocrinology 2015

Endocrine Abstracts (2015) Vol 37
Introduction
Chronic kidney disease secondary to type 2 diabetes is associated with microvascular renal damage. As a result, the prevalence of chronic kidney disease was 31.2% and 11.1% in in patients with diabetes mellitus.

Methods
Retrospective analysis of 60 type 2 diabetic subjects and 30 healthy controls. Diabetics will be transplanted. D2 patients were older than D1 (P < 0.016) but had a lower prevalence of cardiovascular ischemic disease (P = 0.007). No other statistical significant differences were found between the two decades.

Results
Patients in the D2 group had a lower prevalence of cardiovascular ischemic disease (6.1% vs 2.3%, P = 0.016). There was a significant negative correlation between albumin and serum creatinine, and albumin and creatinine ratio measured were.

Conclusion
Diabetic patients admitted in DKTC generally have a long evolution of DM, with several co-morbidities and complications. Even though in the last decade more and older D2 patients were referred to kidney transplant unit, we did not find an increase in those patients complications.

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EP10

Study of irisin hormone level in type 2 diabetic patients and patients with diabetic nephropathy
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Background
Chronic kidney disease secondary to type 2 diabetes is associated with microvascular renal damage. Irisin has been identified recently as an exercise induced hormone secreted by skeletal muscles. It is hypothesised that patients with CKD may have altered irisin levels.

Aim of the work
We aimed to study irisin hormone in type 2 diabetic patient and to assess its relation with diabetic nephropathy (DN).

Subjects and methods
We recruited 60 type 2 diabetic subjects and 30 healthy controls. Diabetics will be divided into 30 patients without complications and 30 with DN. Serum irisin, fasting blood glucose (FBG), 2 h plasma glucose (2 h PG), HbA1c, serum creatinine, and albumin/creatinine ratio were measured.

Results
Irisin was significantly decreased in type 2 diabetic patients compared to control (34.46 ± 15.28 ng/ml vs 152.60 ± 39.58 ng/ml, P < 0.001). Patients with DN had lower irisin than diabetic controls without complications (20.967 ± 4.476 ng/ml vs 47.967 ± 8.853 ng/ml, P < 0.01). There was a significant negative correlation between irisin and systolic blood pressure (r = -0.493), diastolic blood pressure (r = -0.625), serum creatinine (r = -0.729), duration of diabetes (r = -0.942), albumin/creatinine ratio (r = 0.696), BMI (r = -0.396), and HbA1c (r = -0.305) in all diabetic patients. Multivariant regression analysis showed that duration of diabetes is the only independent determinant for irisin level.

Conclusion
There is a decrease in serum irisin level in patients with type 2 diabetes and a further significant decrease in patients with DN.

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EP11

A puzzling bilateral diabetic foot problem
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Introduction
Charcot neuroarthropathy (CN) is a devastating complication of diabetes rapidly leading to irreversible foot deformity when misdiagnosed. Differential diagnosis with foot infections and other foot-related diseases remains challenging.

Case
A 58-year-old woman with type 2 diabetes was hospitalised with a red, swollen left leg and high fever. The diagnosis of erysipelas with a neuropathic wound of the first digit as the entry wound was established. After antibiotic treatment, the infection abated and the patient was discharged. Twelve days later she visited the Emergency Department with increased swelling and pain of the left leg, residual redness and a new skin defect on the left second toe. Ten days later, she was seen at the diabetic foot clinic. The patient reported a recent trauma, which had resulted in pain and a swollen, red right foot. X-rays and a bone scintigraphy with SPECT–CT were performed and surprisingly suggested CN of both feet, a finding that was later confirmed by MRI. A clinically suspected osteomyelitis of the left second digit was ruled out with a leucocyte scan and SPECT–CT. Immobilisation for 3 months with bilateral total contact casts (TCC) was deemed impracticable, so the left foot was treated with an aircast walker instead. Clinically the inflammatory signs subsided but bilateral talar oedema remained noticeable on MRI. Bilateral aircast walkers were advised for another 2 months until custom-made shoes became available.

Conclusion
The diagnosis of an active Charcot foot remains challenging, especially after previous infection or trauma which both may trigger CN. Bilateral CN, although extremely rare, further complicates early diagnosis and efficient bilateral offloading.

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EP12

Continuous subcutaneous insulin infusion decreases hypoglycaemia during nighttime
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Introduction
Continuous subcutaneous insulin infusion (CSII) and multiple daily injections (MDI) are forms of intensified insulin therapy and the most used regimens for type 1 diabetes (T1D). Owing to its continuous basal output, hypoglycaemic events tend to be rarer with CSII. Our goal was to evaluate the differences in nocturnal hypoglycaemia between these two treatment strategies.

Methods
Retrospective analysis of 61 patients who had performed continuous glucose monitoring (Ipro2, Medtronic, Northridge, CA, USA). All patients had T1D and were either on CSII or MDI. Hypoglycaemia was defined as glucose level <70 mg/dl. Daytime (DT) was defined as the period from 0700 to 2300 h and nighttime (NT) was from 2300 to 0700 h.

Results
We obtained 112 714 glucose measurements (42 132 on CSII and 70 582 on MDI). Our sample had mean age of 31.7 ± 8.8 years, BMI of 22.7 ± 5.7 kg/m² and a mean glucose of 156 ± 73 mg/dl. Those on CSII were older (33.0 years vs 31.2 years, P < 0.05), heavier (25.7 kg/m² vs 20.8 kg/m², P < 0.05), and had a higher mean glucose measurement (162 mg/dl vs 154 mg/dl, P < 0.05) than those on MDI. Hypoglycaemia was more frequent in the CSII group (7410 vs 2608 measurements, P < 0.05) and MDI group, particularly at NT period (P < 0.05 for both).

Conclusion
Despite similar HbA1c in the two groups, hypoglycaemia is more frequent in the MDI group, particularly during NT period.

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**EP513**

**Insulin prescription audit**

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Insulin is a life-saving drug but can be life threatening if not prescribed properly. A prospective, consecutive audit of insulin prescription was carried out on all medical and surgical patients admitted to South Tipperary General Hospital with types 1 and 2 diabetes mellitus in November 2013. The practice was compared with hospital guidelines which are consistent with other hospitals nationally. Three prescribing practices were audited: i) the prescription of insulin on insulin prescription sheets (as per hospital policy) or drug kardex; ii) the adjustment of insulin doses on insulin prescription sheets as per blood sugar levels; and iii) the prescription of insulin on discharge prescription. Twenty consecutive patients were audited. 65% had insulin charted on insulin prescription sheet, 15% on drug kardex alone and 20% on both. 80% of patients had their insulin dosage corrected as per blood glucose readings on insulin prescription sheet, 10% on both and 10% did not need insulin dose correction. 60% of patients had insulin prescribed on discharge prescription whereas 40% did not and for the reasons for this were analysed. As a result of these findings a new insulin prescription sheet was recommended and introduced with regular and supplementary insulin sections. Educational sessions on insulin prescription were also organised. A re-audit of a further twenty patients was performed in June 2014 to look at the above three prescribing practices. It showed 100% compliance in terms of insulin prescription. 90% compliance was observed in terms of insulin dose adjustment as per blood glucose readings. The remaining 10% did not require correction of insulin dose. 65% of patients had insulin prescribed on discharge, 10% did not require insulin on discharge, 10% died and 15% were still inpatients at time of re-audit. The re-audit showed an improvement in the practice of insulin prescribing and therefore improved patient safety.

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**EP514**

**Distribution of fat mass in young type 1 diabetic patients**

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**Background**

There is convincing evidence that the increasing of visceral fat is a risk factor for vascular disease. Type 1 diabetes mellitus (T1DM) is characterized by the development of micro-, and later, and macrovascular complications. The aim of the study was to examine features of body composition fat distribution parameters in T1DM patients.

**Materials and methods**

96 patients with T1DM (59 women and 37 men) (mean age: 32.52 ± 10.71 years, duration of DM: 12 (7.5–20) years, age of manifestation: 18 (13–23.5) years, BMD: 23.47 ± 3.16, HbA1c: 8.45 ± 1.2% and 54 (30 women and 24 men) controls matched for age, sex, and BMI were examined. Body composition was determined by dual energy X-ray absorptiometry.

**Results**

Fat mass parameters in T1DM males and controls males were: android fat: 27.41 ± 11.43% vs 28.9 ± 9.67% (P = 0.627), gynoid fat: 28.06 ± 7.15% vs 26.74 ± 7.74% (P = 0.506), A/G ratio: 0.95 ± 0.24 vs 1.06 ± 0.15 (P = 0.048); total body: 23.02 ± 7.9% vs 22.55 ± 7.5% (P = 0.819); trunk/total: 0.51 ± 0.07 vs 0.54 ± 0.034 (P = 0.094); legs/total: 0.35 ± 0.06 vs 0.32 ± 0.032 (P = 0.93); and (arms + legs)/trunk: 0.59 ± 0.28 vs 0.77 ± 0.105 (P = 0.034). Similar features in T1DM women and controls women were: android fat: 32.29 ± 8.44% vs 32.37 ± 10.81% (P = 0.97); gynoid fat: 41.72 ± 6.63% vs 41.36 ± 7.16% (P = 0.81); A/G ratio: 0.76 ± 0.14 vs 0.45 ± 0.05 (P = 0.97); total body: 33.25 ± 6.7% vs 32.3 ± 7.59 (P = 0.551); trunk/total: 0.44 ± 0.08 vs 0.45 ± 0.056 (P = 0.611); legs/total: 0.412 ± 0.05 vs 0.415 ± 0.054 (P = 0.812); and (arms + legs)/trunk: 1.18 ± 0.25 vs 1.17 ± 0.3 (P = 0.837). Gynoid (peripheral) fat distribution was positively correlated with the age of T1DM males (r = 0.19; P = 0.018), however no correlation was found with the duration of the disease, level HbA1c, the total daily insulin dose.

**Conclusions**

The peripheral type of fat mass distribution is dominated at T1DM males compared with control, while there were no differences in the distribution of adipose tissue among the investigated women. The obtained data indicate gender differences in the distribution of fat mass in T1DM patients.

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**EP515**

**Roux-en-Y gastric bypass reduces proteinuria in diabetic kidney disease to a greater extent than weight loss alone in the Zucker diabetic fatty rat without a greater improvement in renal inflammation**

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**Background**

The effect of Roux-en-Y gastric bypass (RYGB) on diabetic kidney disease (DKD) is unclear. We used a Zucker diabetic fatty rat (ZDF) model of DKD to determine the effect of RYGB on histopathological markers of DKD, proteinuria, and MCP1 excretion.

**Methods**

ZDF rats underwent RYGB (n = 15) or sham surgery (n = 14) at 18 weeks of age. Eight sham operated animals were food restricted to match the weight loss of the RYGB group (body-weight matched (BWM) group). Animals were sacrificed at age 31 weeks.

**Results**

Macrophage infiltration (ED1 staining), urinary MCP1:creatinine ratio and MCP1 expression was reduced by in both RYGB and BWM groups (P < 0.05). Despite similar effects on inflammation, RYGB had a greater effect on reducing proteinuria (P = 0.01).

**Conclusions**

Weight loss alone can remediate renal inflammation, but RYGB has a greater effect on proteinuria. This may be due to other mechanisms such as incretin effects.

**Disclosure**

This work was supported by Science Foundation Ireland ref 12/YI/B2480.

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**EP516**

**Assessment of the myelin damage degree in patients with and without diabetic neuropathy**

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**Background and aims**

Diabetic neuropathy is associated with impaired neuron myelination, nerve conduction, and muscle function. The pathogenic mechanisms of reduced myelination in diabetes mellitus are poorly understood. Peripheral myelin protein 22 (PMP22) is glycoprotein with proposed roles in peripheral nerve myelin formation. This study allows us to consider the changes in the plasma levels of PMP22 in patients with and without diabetic neuropathy.

**Materials and methods**

We studied 34 subjects with DM duration of 15.2 ± 2.1 years, mean value of HbA1c was 8.4 ± 1.2% divided into two groups: diabetic patients without symptoms of peripheral somatic neuropathy (PSN) (consisted of 12 participants (five males/seven females), mean age was 42.7 ± 10.1 years) and patients with diabetes and confirmed diagnosis of diabetic PSN (22 patients (eight males/14 females), mean age was 42.8 ± 10.1 years) and 20 healthy volunteers (nine males/11 females, mean age was 48.3 ± 9.5 years) as the control group. The plasma concentrations of PMP22 were measured by immunoassay. No subjects studied had signs of other disorders of peripheral nervous system.

**Results**

We found that plasma levels of PMP22 were significantly higher in the patients with PSN (9.1 ± 1.32 ng/ml) compared to diabetic subjects without PSN (3.8 ± 0.15 ng/ml) and control group (1.53 ± 0.31 ng/ml), P < 0.05.

**Conclusion**

These findings could suggest the occurrence of the neuron demyelination reflected by the elevated PMP22 in patients with diabetic neuropathy.

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GDM on dry eye parameters. Although, GDM cause many negative consequences to the best of our knowledge, there is no study in the literature about the effects of GDM group (105.17 ± 6.05 mg/ml and 7.28 mg/ml and 5.57 ± 0.50%) compared to healthy group 8.66 points in GDM group, and 12.33 ± 2.16 s, 308.36 ± 14.80 mOsm/l and 9.59 ± 0.69 points in GDM group, and 12.33 ± 5.33 mm, 5.67 ± 2.68 s, 308.36 ± 16.00 mOsm/l and 10.62 ± 8.66 points in healthy group. There were not statistically significant differences between two groups. There were not statistically significant differences in any of the tear function tests such as Schirmer, tear break-up time (TBUT), tear film osmolarity (TFO), and ocular surface disease index (OSDI) score in pregnant with GDM.

Methods
Pregnant women with GDM and healthy pregnant who were matched in both age and gestational age were enrolled into the study. The women with ocular or systemic disorders that may affect the tear function tests, and who use topical medications were excluded from the study. All of the pregnant answered the OSDI questionnaire, afterwards they underwent a detailed ophthalmic examination including Schirmer, TBUT, and TFO by the same ophthalmologist.

Results
Forty-six pregnant with GDM whose mean age of 30.43 ± 4.75 years and 36 healthy pregnant whose mean age of 28.83 ± 4.42 years were enrolled into the study. The mean gestational ages were 25.80 ± 1.61 and 26.19 ± 1.43 weeks respectively. There were not statistically significant differences between two groups in terms of age and gestational age. The mean fast blood glucose and the mean HbA1c levels were statistically significantly higher (P < 0.001, for each) in GDM group (105.17 ± 7.28 mg/dl and 5.57 ± 0.50%) compared to healthy group (70.17 ± 6.54 mg/dl and 4.93 ± 0.29%). The levels of Schirmer test, TBUT test, TFO, and OSDI score were 11.20 ± 4.93 mm, 5.59 ± 2.16 s, 309.65 ± 14.80 mOsm/l and 9.59 ± 0.69 points in GDM group, and 12.33 ± 5.33 mm, 5.67 ± 2.68 s, 308.36 ± 16.00 mOsm/l and 10.62 ± 8.66 points in healthy group. There were not statistically significant difference in any of the tear function tests between two groups.

Conclusions
To the best of our knowledge, there is no study in the literature about the effects of GDM on dry eye parameters. Although, GDM cause many negative consequences on pregnant women, it seems to be no negative effects on tear function tests.

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The impact of non-alcoholic fatty liver disease on carotid artery intima-media thickness as a risk factor for atherosclerosis

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Introduction
Non-alcoholic fatty liver disease (NAFLD) is considered a hepatic manifestation of metabolic syndrome and is closely associated with abdominal obesity, atherogenic dyslipidaemia, and diabetes exposing subjects with NAFLD to an increased risk of developing cardiovascular disease. The aim of this study is to determine the prevalence of NAFLD in diabetes mellitus (DM) patients, to correlate it to the subclinical atherosclerosis in these patients.

Description of method
One hundred and twenty-four consecutive patients with type 2 DM were enrolled. NAFLD was diagnosed using fatty liver index (FLI), an algorithm based on BMI with alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase, and triglycerides. Carotid atherosclerosis (intima-media thickness (IMT)) was evaluated by high-resolution carotid B-mode ultrasonography. Plasma liver function tests and other biochemical blood measurements were determined.

Results
Patients were divided into three groups; G1: FLI < 30 (n = 56); G3: FLI > 60 (n = 40); and G2: intermediate group (n = 28). The prevalence of NAFLD using FLI ≥ 60 in DM patients was 40 patients (32%) C IMT increased with FLI (G1: 0.54 ± 0.08 mm vs G2: 0.40 ± 0.08 mm, P < 0.0001). FLI was associated with increased LDL cholesterol (r = 0.38), alanine aminotransferase (r = 0.55), BMI (r = 0.34), diastolic blood pressure (r = 0.41) and triglycerides (r = 0.49), and reduced HDL cholesterol (r = -0.52) and insulin resistance (r = -0.30, all P < 0.0001). The correlations hold also in multivariate analysis after adjusting for age and gender. Behavioural variables (smoking and diet) and fasting plasma glucose, did not significantly differ between subjects with and without FLI.

Conclusion
NAFLD increases the risk of subclinical atherosclerosis in DM patients. DM patients with NAFLD in our study showed significant correlation with cardiovascular risk factors.

Disclosure
European Social Found, Houman Resources Development Operational Programme 2007–2013, project no. POSDRU/159/1.5.1/338776.

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Self-monitoring of blood glucose patterns among Turkish diabetic patients

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Self-monitoring of blood glucose (SMBG) increases life expectancy and improves diabetic patients’ quality of life. 17 type 1 diabetic patients and 159 type 2 diabetic patients’ files were randomly evaluated to evaluate SMBG practice patterns in our hospital. All type 1 patients used insulin, while 38 type 2 diabetic patients used drug only, 35 type 2 diabetic patients used drugs in combination with insulin and 86 type 2 diabetic patients used insulin only. 90.3% of our patients owned a glucometer. Although, this high percentage one of the type 1 and nine of the type 2 diabetic patients did not practice SMBG despite owning a glucometer. 23.5% of type 1 diabetic patients and 47.2% of type 2 diabetic patients only measured their fasting glucose levels. 11.8% of type 1 diabetic patients and 4.4% of type 2 diabetic patients only measured their postprandial glucose levels. 58.8% of type 1 diabetic patients and 40.9% of type 2 diabetic patients measured fasting and postprandial glucose levels. Only a minority (33.3%) of those using insulin did not practice SMBG. 31 patients reported to examine their blood glucose levels if they were symptomatic. 20 patients monitored their blood glucose weekly, three patients once monthly and 15 every second day. Seven diabetic patients measured fasting and postprandial glucose levels. 58.8% of type 1 diabetic patients and 40.9% of type 2 diabetic patients did not practice SMBG despite checking postprandial glucose levels. In summary the majority of our patients does not perform SMBG levels adequately and do not adjust their medicament doses or insulin doses.

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New-onset diabetes after renal transplantation (NODAT) and nodular glomerulosclerosis of the renal allograft

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EP521

Sexual functioning and distress in types 1 and 2 diabetic women: a two-centres experience

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Introduction

A high prevalence of sexual disorders has been observed in women with types 1 and 2 diabetes mellitus (DM). Here we present 4 years, two-center results of the study of disorders of female sexual functioning in female patients with diabetes.

Materials and methods

During the period 2011–2014, female DM patients and healthy controls were enrolled according to the protocol inclusion criteria. The FSFI, FSIDS, and GHQ-28 questionnaires were used to evaluate sexual functioning, sexual distress, and general health respectively. Comparative and regression tests were used to analyse data.

Results

In total, 221 patients and 218 healthy controls were enrolled. Of the 221 patients, 107 (48.4%) had a diagnosis of T1DM and the remaining 114 (51.6%) had T2DM. Control group was divided to CG-1 and CG-2 (104 and 114 women respectively) subgroups, each one age matched for T1DM and T2DM subgroups.

Diabetic patients in general, had significantly lower FSFI and higher FSIDS scores compared to the healthy controls (P<0.05). T1DM and T2DM women also had significantly lower FSFI and higher FSIDS scores compared to CG-1 and CG-2 controls (P<0.05).

Diagnosis of ‘any’ diabetes, was found to be a significant predictor of FSD (OR 2.746, P<0.05). T1DM and T2DM women were 2.698 and 2.887 times more likely to have FSD compared to CG-1 and CG-2 non patients respectively (P<0.05). Psychosocial factors, mainly depression, were found to be significant determinants for FSD in diabetic and non diabetic women (P<0.05).

Conclusion

The current study findings confirm that FSD is more prevalent in women with diabetes. Both types of diabetes were found to be significant determinants for FSD in the patients of our study. Moreover, the role of psychosocial factors, such as depression, in the pathogenesis of sexual disorders and distress in both diabetic and non-diabetic women is highlighted.

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EP522

Association of SNPs in the intergenic region of OCT2 and OCT3 with short-term efficiency of metformin monotherapy in the type 2 diabetes patients

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Clinical response to metformin is highly variable in type 2 diabetes (T2D) patients highlighting the need for identification of genetic components affecting the efficiency of metformin therapy. Aim of this study was to evaluate the role of systematically selected tagSNPs from genomic regions coding for six organic cation transporters implicated in transport of metformin with respect to the short-term efficiency. The study involved 102 drug naïve newly diagnosed T2D patients who were treated with metformin monotherapy for 3 months. We genotyped 104 tagSNPs from six metformin transporter genes coding for OCT1, OCT2, OCT3, MATE1, MATE2, and PMAT. Minor alleles of rs3119309, rs7757336, and rs2481030 located in the intergenic region between SLC22A2 (OCT1) and SLC22A3 (OCT3) were significantly associated (P=1.849×10^-6 to 2.663×10^-5) with metformin inefficiency defined as no decrease of Hba1c blood level after 3 months of treatment. Carriers of risk alleles were 8.4 times more likely to exhibit non-responder phenotype than participants with wild type alleles.

Pharmacokinetic study in 15 healthy participants was conducted to investigate the effects of identified polymorphisms on kinetics of plasma and erythrocytes metformin after acute administration in healthy subjects. Subjects with combined risk alleles of polymorphisms rs3119309, rs7757336, and rs2481030 located in the intergenic region between SLC22A2 (OCT1) and SLC22A3 (OCT3) were significantly associated (P=1.849×10^-6 to 2.663×10^-5) with metformin inefficiency defined as no decrease of Hba1c blood level after 3 months of treatment.

In conclusion, there was progressive graft dysfunction despite good glycemic control, with confirmed nodular glomerulosclerosis typical lesions. Thus, in the NODAT with renal allograft dysfunction, it is not excluded the possibility of association with diabetic nephropathy. This case also shows that in NODAT there are the same risk factors for the occurrence of late diabetic complications.

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EP523

Abstract withdrawn.

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EP524

Hyperosmolar hyperglycaemic state and diabetic ketoacidosis: a 5-year retrospective study in a university hospital

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Introduction

Hyperosmolar hyperglycaemic state (HHS) and diabetic ketoacidosis (DKA) are the two most serious acute metabolic complication of diabetes mellitus (DM). The authors propose to characterise the admissions for HHS and DKA at a university hospital.

Methods

An observational, descriptive, and retrospective study in adults admitted to the hospital between January 2009 and October 2013 due to HHS and DKA. The information was accessed via the patients’ electronic records. Statistical analysis was carried out using SPSS.

Results

71 patients were admitted with HHS, with a dominance of female patients (62%). The median age was 79 years and 38% were considered to have economic difficulties. A quarter of the patients was unaware they were diabetic. The most common clinical manifestation on admission was prostration (65%) and the precipitating factor infections (47%). On admission, 25% were treated with insulin but when they became orientated this percentage went up to 62%. During their admission, 41% of the patients were referred to endocrinology. The median time of stay was 9 days. One year after discharge, 11% of patients had been readmitted for the same reason and 23% had passed away.

In the case of DKA, 44 patients were admitted, 63% being female patients. The median age was 57 years and 51% were considered to have economic difficulties. Half the patients presented with prostration and in 35% of the cases the precipitating factor was lack of compliance with therapy. The median time of stay was 8 days. A quarter of the patients had already had a previous admission and a year after discharge, 30% had been readmitted for the same reason whilst 22% had passed away.

Conclusion

In 5 years, 115 patients were admitted with acute complications of DM. The high incidence of readmissions and mortality in the year following discharge as well as the lack of the compliance with therapy in those admitted with DKA are noteworthy. This shows a need for improved assisted care post-discharge in these patients.

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EP256

Bone mineral density in patients with type 1 diabetes mellitus by DEXA and QCT

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Introduction

Type 1 DM (T1DM) has been associated with low bone mineral density (BMD) measured by dual energy X-ray absorptiometry (DEXA) but not with quantitative computed tomography (QCT). QCT provides a three-dimensional image and measures bone’s volume directly as density, independent of the surrounding tissues. The purpose of this study was to evaluate BMD in patients with T1DM using DEXA and QCT.

Methods/design

We studied 81 patients with T1DM (group D) (age: 36±9.7 years, M/F: 32/49) and 70 healthy controls (group C) matched for age, sex, and BMI. In both groups, we measured HbA1c, lumbar spine (LS), and femoral neck (FN) BMD by DEXA and LS BMD by QCT.

Results

Mean BMI (kg/m²) was similar in both groups (D: 23.3±8.1 vs C: 23.7±8.3, P=0.39). In group D, mean duration of diabetes was 16.1±9.9 years and mean HbA1c was 8.1±1.3%. BMD (g/cm²) and z-score measured by DEXA were lower in group D compared to group C at LS (1.02±0.20 vs 1.05±0.14, P=0.03) (-0.31±1.61 vs 0.78±1.76, P=0.01) and at FN (0.69±0.12 vs 0.89±0.11, P=0.043) (-0.14±1.71 vs 1.35±1.04, P=0.037). Also, LS z-scores measured by QCT were lower compared to DEXA (D: -0.16±1.08 vs -0.31±1.61, P=0.022). The lower DEXA z-scores were negative correlated with young onset age (r=−0.74, P=0.021) and longer duration of T1DM (r=−0.78, P=0.032) but not with glycaemic control (r=0.36, P=0.18). In group D, DEXA detected 9/81 patients (11.1%) with osteopenia and 1/81 with osteoporosis (1.2%) at LS and 5/81 (6.2%) with osteopenia and 1/81 with osteoporosis (1.2%) at FN. In contrast, QCT has detected 14/81 patients (17.3%) with osteopenia and 2/81 patients (2.5%) with osteoporosis at LS.

Conclusion

T1DM is associated with lower BMD compared to controls with both methods used. The choice of measuring method may define a different degree of bone loss.

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EP257

Is early measurement of HbA1c useful for the prediction of treatment response in type 2 diabetes?

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HbA1c, which is correlated with 3-month mean glycaemia, is usually measured every 3–6 months. Effects of variations of treatment are routinely assessed through HbA1c not earlier than 3 months. Glycated albumin (GA) has been proposed as an indicator of shorter-term (2-week) glucose control Aim of the present pilot study was to explore the possibility of predicting 3-month HbA1c by measuring HbA1c or GA at 15–30 days. Twenty-seven metformin-treated patients with type 2 diabetes initiating a pharmacological treatment other than insulin were enrolled after written informed consent. The patients (16M:11F, aged 64.7±10.1 years) had a duration of diabetes of 8.6±5.8 years, baseline HbA1c 57.0±12.0 mmol/mol. The prescribed treatment was maintained throughout the 3-month follow-up. HbA1c and GA were measured at baseline, 15, and 30 days, and HbA1c only at 90 (±3) days. HbA1c at 90 days (50.0±7.2 mmol/mol) was significantly (P<0.001) reduced from baseline (59.0±12.0 mmol/mol). A significant reduction was already present at 15 days (56.7±7.8 mmol/mol, P<0.001) and confirmed at 30 days (53.0±7.0 mmol/mol, P=0.001). A similar pattern was found for GA, which was significantly lower at 15 (28.8±10.8%, P=0.03) and 30 (27.0±9.8%, P=0.001) days than at baseline (31.9±11.3%). Variations of both HbA1c and GA at 15 days showed a significant correlation with 90-day variation of HbA1c: R=0.895, P=0.001 and R=0.418, P=0.030, respectively, confirmed at 30 days. The early identification of patients
Diabetic polynuropathy is the most prevalent complication of diabetes. Diabetic foot lesions become limb threatening from a combination of injury, infection and impaired micro and macrocirculation. When diabetic patients go on holiday they usually change their routine and may become careless in routine care of their feet. We report a case series of seven middle aged Irish born diabetic male patients who developed serious foot lesion on holiday. They were identified from the podiatry services of a regional centre over 3 years. The median age was 59, range 37-68 years. Six of seven had type 2 diabetes duration 1–30 years. HbA1c ranged from 7 to 10.6%, median: 9.6%. One smoked. All had signs of peripheral polynuropathy. Two had Charcot joint. Six of seven had a holiday in a warmer climate. The median delay to seeking care was 2 weeks, range 1 day–12 weeks. Lesions had a variety of sites, they were bilateral in 5/7. Lesions included: massive blister, ulceration, pressure necrosis, and maceration. Infection was present in six of seven. Two of seven required partial foot amputation. Two had a hospital stay over 60 days. Healing took 4–20 weeks. All walked more than usual for their customary habit and often on uneven surfaces. One walked barefoot for a week incurring deep planter ulceration. Another wore tight golf shoes incurring pressure necrosis. One walked extensively in an orthopaedic boots. The majority wore sandals resulting in tissue maceration and infection. All reported heat as an aggravating factor. Middle-aged diabetic males with polynuropathy seem particularly vulnerable on holiday. The common factors were: i) a change in or inappropriate footwear, ii) uncustomed walking and surfaces, and iii) heat causing tissue maceration. Patient education should emphasise the hazards of holidays in high-risk patients.

**EP528**

Sex steroids levels and body composition in male patients with type 1 diabetes mellitus

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Introduction

Limited data exists regarding testosterone levels in type 1 diabetes mellitus (T1DM). The objective of this study was to evaluate serum sex steroids levels and body composition using dual energy X-ray absorptiometry method (DEXA) in male patients with T1DM.

Methods/design

We studied 36 male patients with T1DM (group D) (age: 35.3 ± 11.66, years) and 35 healthy control (group C) matched for age, sex, and BMI. In both groups waist circumference (WC), HbA1c, total testosterone (TT), sex hormone-binding globulin (SHBG), LH, FSH, and IGF1 were measured. Calculated free (cFT) and bioavailable testosterone were estimated by standard formulas. Moreover, body composition was determined by DEXA and was calculated central abdominal fat (CAF). Results

Mean BMI (kg/m²) and mean WC (cm) were similar in both groups (D: 25.8 ± 3.44 vs C: 25.2 ± 3.2, P = 0.37) and (D: 94.5 ± 9.6 vs C: 92.9 ± 8.7, P = 0.24). In group D, mean duration of DM was 16.8 ± 10.5 years and mean HbA1c was 8.2 ± 1.1%. We did not observe significant difference in TT, LH, and FSH levels between two groups. Group D had significantly lower SHBG (nmol/l) and IGF1 (ng/ml) levels than group C (39.57 ± 7.5 vs 37.32 ± 6.9, P = 0.043 and 144.7 ± 30.1 vs 180.2 ± 27.1, P = 0.031). Lower cFT (nmol/l) and bioT (nmol/l) levels were observed in group D compared to C but did not reach clinical significance (0.608 ± 0.136 vs 0.812 ± 0.119, P = 0.052 and 14.7 ± 2.3 vs 15.2 ± 2.5, P = 0.057). Total fat and CAF were similar in both groups. CAF was negative correlated to TT and FT levels (r = -0.73, P = 0.029 and r = -0.79, P = 0.034). In group D, 2/36 (5.6%) had TT levels below the normal range after adjustment for age and BMI but none of group C.

Conclusion

Patients with T1DM seem to have a tendency to hypogonadism and its existence mainly occurred in association to obesity.

**EP529**

Diabetic ‘holiday’ foot: cautionary tales of sun, sandals, and risk

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Maladies of the feet are common in diabetic patients; particularly vulnerable on holiday. The common factors were: i) a change in or inappropriate footwear, ii) uncustomed walking and surfaces, and iii) heat causing tissue maceration. Patient education should emphasise the hazards of holidays in high-risk patients.

**EP530**

Macrovacular complications in type 1 diabetes mellitus

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Introduction

Cardiovascular complications are well known in type 2 diabetes with other factors of cardiovascular disease. Recently, with the intensive treatment of type 1 diabetes, many studies have focused on macrovascular complications in type 1 diabetes. The aim of our study was to determine the long-term cardiovascular risk factors and macrovascular complications in type 1 diabetic patients.

Patients and methods

A retrospective study involving 45 patients hospitalised in Rabta Endocrinology Department between 1997 and 2005 for type 1 diabetes. We noted after a minimum follow-up of 10 years the appearance of cardiovascular events. We also reported cardiovascular risk factors such as family history of cardiovascular events, smoking, obesity, dyslipidaemia, and hypertension, insulin dose, and glycaemic control.

Results

Our patients were 21 men and 24 women. The average age of our patients at diagnosis was 25.3 years (10–50), their mean BMI was 22 (15.8–26.95). The average waist circumference was 75.88 cm. Ten patients were smokers, four patients had a family history of cardiovascular events. The lipid profile was normal in all patients. The mean insulin dose was 1 UI/kg per day (0.16–1.54). The mean duration of diabetes in our patients was 14 years (range 10–30). Six patients developed hypertension. After a follow-up of 10 years, the mean BMI was 20 (18.19–38) and the mean insulin dose was 1 UI/kg per day. The mean of HbA1c was 10%. We didn’t report any macrovascular events in our patients.

Conclusion

Type 2 diabetes is usually associated with other cardiovascular risk factors related to the metabolic syndrome. Poor glycaemic control is a common factor to both types 1 and 2 diabetes. Comprehensive prevention beyond glycaemic control is necessary to prevent the occurrence of cardiovascular events in type 1 diabetes.

**ENDOCRINE ABSTRACTS**

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**EP531**

Is dyslipidaemia adequately controlled in type 2 diabetes in primary care? Analysis of 183 patients

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Objectives
To evaluate the degree of control of atherogenic dyslipidaemia in patients with type 2 diabetes mellitus (T2DM).

Methods
Retrospective cohort study which included patients with T2DM followed in a primary care setting. Patients were classified according to the following criteria: strict control of dyslipidaemia (LDL_c < 100 mg/dl and triglycerides < 150 mg/dl), partial control of dyslipidaemia (LDL_c ≥ 100 mg/dl or triglycerides ≥ 150 mg/dl), or absence of control of dyslipidaemia (LDL_c ≥ 150 mg/dl and triglycerides ≥ 150 mg/dl). Treatment with lipid-lowering drugs (statins, fibrates, nicotinic acid, and ezetimibe) was also collected.

Results
183 patients were included, with a mean age of 62.1 ± 8.3 years (58.4% women). After stratification of patients according to previous criteria, only 32% of patients had strict control of dyslipidaemia, 43% had partial control of dyslipidaemia, and 25% had absence of control of dyslipidaemia. Associated lipid-lowering treatment was present in 72% of patients with strict control, in 81% of patients with partial control and in 90% of patients with absence of control.

Conclusions
Despite the high rate of lipid-lowering therapy in patients with T2DM, a significant percentage of patients do not achieve recommended lipid goals.

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**EP532**

Evaluation of plantar pressure and force in diabetes using Tekscan F-Scan in-shoe foot force and gait analysis system

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Background
Evaluation of plantar pressure is useful for detecting functional abnormality of foot, especially in diabetic patients. The aim of this study was to evaluate plantar pressure and force in diabetic patients using Tekscan F-Scan in-shoe foot force and gait analysis system.

Methods
Plantar pressure and force were measured by selecting an area of interest under the six areas of the foot: hallux, first metatarsal, second metatarsal, 3–5 metatarsal, midfoot and heel based on previous reports. 65 diabetic patients and age-matched 25 controls were enrolled. Mean age of diabetic patients was 58.4 ± 8.2 years, diabetic duration 8.39 ± 5.26 years, and mean HbA1c 7.7 ± 1.3%, and female 43.1% (26/65). Of the included 65 patients, 16 had diabetic polyneuropathy (DPN), 12 had cardiac autonomic neuropathy (CAN), 31 were without CAN, and 18 had inconclusive tests.

Results
Contact area distribution in diabetics were higher tendency than those in controls. Maximum force distribution was different between two group nearly all areas of foot, especially second metatarsal (109.4 N in DM vs 72.2 N in control, P < 0.001) and condyle (307.4 N in DM vs 236.9 N in control, P < 0.001). Pressure average distribution were similar differences between two groups. Right-to-left foot unbalancing of force and pressure in diabetics were showed compared with controls.

Conclusion
Evaluation of plantar pressure is useful for diabetic foot abnormalities. Plantar force and pressure distributions in diabetics are higher than those in controls, especially, in second metatarsal and condyle area. This method may be useful to detect diabetic foot and ulcerative disease early.

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**EP533**

Knowledge assessment of diabetic patients about their disease: a prospective study

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Introduction
Therapeutic education of diabetic patients is an integral part of management care of the disease and a permanent way to empower patients and to promote their self-care. The purpose of this study is to evaluate the knowledge of diabetic patients about their disease.

Patients and methods
This prospective study has been conducted during 9 months and included 312 patients with type 2 diabetes mellitus (T2DM) diagnosed at least 3 months ago. All patients were followed in third care consultation without history of structured education program. Clinical and biological data in addition to an Individual Knowledge Scale (SKILLD). A value above 50% reflects a good level of knowledge.

Results
The mean age was 54-year-old and 61% of patients were males. The average of T2DM history was of 11 years with a mean HbA1c of 9.35 ± 1.85%. Symptoms of hypoglycaemia were known by 58% of patients, but its immediate management was only known by 41% of patients. Education on lifestyle rules revealed poor knowledge in 67% of our patients. HbA1c target was unknown in 82% of patients. The average score on SKILLD was at 37 ± 26%. A score > 50% was observed in 32.4% of patients. SKILLD value was positively correlated with education level (r = 0.661, P < 0.001), and negatively correlated with duration of diabetes and HbA1c (r = −0.384; P < 0.001 and r = −0.497; P < 0.001 respectively). Patients with low SKILLD scores had significantly higher HbA1c (9.78% vs 8.45%, P < 0.001) and higher age (54.07-year-old vs 40.55-year-old, P < 0.001) compared to patients with high SKILLD score.

Conclusion
Our study shows knowledge lack about diabetes. This may reflects the difficulty of education during consultation probably because time limitation. We insist through these results on the need of a complementary structured and multidisciplinary therapeutic education.

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**EP534**

Diabetic foot infection: study of 109 patients

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Introduction
Diabetic foot infection (DFI) is a major public health problem, both for its morbidity and mortality and the economic social cost due to repeated hospitalisations and the high rate of amputation.

Objectives
Analyse the clinical presentation of DFI, study risk factors of developing this infection and describe the therapeutic management.

Materials and methods
Retrospective study spread over 8 years old, of 109 patients hospitalised in the University Hospital of Endocrinology of Sfax and who had a DFI.

Results
The average age of patients was 57.5 years (25–82). Sex ratio was 2.02. Most patients were type 2 diabetes (87.2%) with diabetic history of more than 15 years in 34% of cases. A history of hospitalisation for diabetic feet before the study period was found in 39.4%. On admission diabetes were poorly controlled in the majority of our patients. Among the chronic microangiopathic complications, we found neuropathy (64.2%), nephropathy (20.2%), and retinopathy 37.6%. Macroangiopathic complications were dominated by arteriopathy of the lower limbs in 20.2%. The DFI were unique or multiple. It was ‘non-threatening member’ infection in 64.2%, dominated by infected wounds in 57.1%. The infection was severe, dominated by infected gangrene in 33%, followed by infected plantar ulcer in 22%. Samples for bacteriological test were performed in 29 patients. The bacteria involved were dominated by Staphylococcus 20.7% and gram-negative bacteria in 17.2%. 105 of our patients received an antimicrobial. The association amoxicillin–clavulanic acid +/− ciprofloxacin were prescribed in first intention in 47%. The average duration of antibiotic therapy was 9.7 days in case of infection ‘non-threatening member’ and 17.3 days for severe infection.

Surgical treatment was performed in 45%. Conservative treatment or amputations were done in 15 and 30% cases respectively.

Conclusion
Prevention is the only way to reduce morbidity caused by lesions of the diabetic foot.

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EP535
Diabetes and ischaemic stroke: prospective study in hospitalised patients
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Introduction
Diabetes mellitus (DM) is a major risk factor for stroke and has been shown that diabetic patients who suffer stroke have a worse prognosis, with greater morbidity and mortality.

Objectives

Methods
Observational, analytical, and prospective study of hospitalised patients for ischaemic stroke in Hospital de Braga between August and November 2013. Statistical analysis: SPSS v.20.

Results
Of the 134 patients, 30.6% had a previous diagnosis of DM, 79.9% were over 65 years, and 53.7% were women. The median age was 79 years with no statistical significance between groups (P = 0.624). The median blood glucose at admission was 115 mg/dl, with statistical significance between groups (156 mg/dl vs 108 mg/dl; P < 0.005). The median hospital stay was 10 days for both groups. Although, not statistically significant, the prevalence of neurological and infectious complications was lower in diabetic patients (24.4% vs 36.6%; P = 0.167) as well as in hospital mortality (2.4% vs 10.8%; P = 0.106). There was no statistical significance between blood glucose on admission, prevalence of complications and in-hospital mortality. In the group of diabetic patients, the median HbA1c was 7.2%. There was no statistical significance between glycaemic control (HbA1c) and prevalence of complications or in-hospital mortality. About DM treatment at admission vs discharge: 61.0% vs 56.1% vs treated with oral antidiabetics (OA), 17.1% vs 17.1% with insulin and OA, 9.8% vs 24.4% only with insulin, and 12.2% vs 2.4% without drug therapy.

Conclusion
Glycaemic control in the diabetic group is reasonable, in most patients, assuming the age, pre-existing comorbidities and chronic complications. We admit that the absence of a higher prevalence of complications and mortality in diabetic vs non-diabetic group, may be related to the small sample size.

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EP536
Renal disease risk in type 2 diabetic patients with metabolic syndrome
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Background
Patients with diabetes mellitus (DM), diabetic nephropathy (DN), and metabolic syndrome (MS) have a high risk of cardiac morbidity and mortality. Thus, identifying and treating risk factors associated with cardiovascular disease in DM may offer the best approach for preventing and delaying adverse renal and cardiovascular outcomes.

Aim
To determine the relationships between MS, DN, and renal function in type 2 DM.

Methods
In our clinic-based cohort study were enrolled 216 type 2 diabetic patients, from which 59% males and 41% females, with a mean age 54 ± 10 years. We analysed MS, detected DN, and estimated glomerular filtration rate (eGFR) during a 4 years period.

Results
Prevalence of both microalbuminuria and macroalbuminuria were higher in subjects with MS than in those without it (84 ± 12 ml/min per 1.73 m² vs 90±21 ml/min per 1.73 m²; P < 0.001). The lowest eGFR values were found in those with four or more components of MS. Prevalence of low eGFR increased with the stage of DN and was affected by MS only in normoalbuminuric patients. The most important result was that MS was independently associated with DN, but not with low eGFR, after adjustment for all of the individual components of the MS.

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Conclusions
In this study we have noted an independent association between MS and DN. This is a strong argument for treating the MS by an intensive therapy, in order to prevent the progression of DN to the renal failure.

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EP537
Optimal regimens of the basal-bolus insulin therapy in adolescents with diabetes mellitus of type 1
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To achieve the optimal glycaemic control in adolescents with type 1 diabetes mellitus (DM1) is a difficult task. The reason is a low compliance of teenagers caused by psychoemotional peculiarities as well as decreased insulin sensitivity due to a physiologically high concentration of contrainsular hormones (androgens, GH, etc.). This study was aimed to determine peculiarities in regimens of the pump insulin therapy that are necessary for achieving treatment goals in adolescents with DM1. 68 adolescents at the age of 14–18 with DM1, who received continuous subcutaneous infusion of insulin (CSII) from 6 months to 6 years, were examined. The patients were subdivided into two groups: i) adolescents with the optimal and suboptimal metabolic control (n = 46) and ii) adolescents with long-standing poorly controlled DM1 (n = 22). Compared with patients in group 2, adolescents in group 1 had significantly higher average total daily dose of insulin (group 1 – 70.0 (53.2; 83.8) U and group 2 – 54.0 (46.3; 68.4) U, P = 0.038), average daily dose of basal insulin (group 1 – 35.2 (24.7; 40.8) U and group 2 – 25.2 (22.7; 32.7) U, P = 0.019). The average basal-to-bolus ratio from group 1 patients was 51/49%, compared with Group 2 patients 45/55%. Prevalence of bolus insulin in adolescents with poorly controlled DM1 was caused by frequent use of correction boluses in order to lower postprandial hyperglycaemia resulting from the excessive intake of carbohydrates. Group 2 patients had a low level of skills which did not allow them to use additional functions of the pump. A large part of group 1 patients adapted pump settings on their own according to their individual peculiarities, physical activity, etc. Thus, well-balanced basal-to-bolus ratio in adolescents on CSII, which can provide improvements in blood glucose management is 51/49%. An important condition is also a high level of compliance and skills of patients, intention to control actively the disease.

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EP538
Contribution of haptoglobin and MTHFR polymorphisms to hyperhomocysteinemia and hypercysteinemia in type 2 diabetic patients
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Introduction
There is a lack of epidemiological data on the distribution of haptoglobin and C677T of MTHFR polymorphisms in Caucasians type 2 diabetic patients. The contribution of these two genetic factors to hyperhomocysteinemia and hypercysteinemia can be useful to prevent cardiovascular events and to reduce public health costs. The aim of this study is to evaluate the contribution of haptoglobin and C677T polymorphisms for hyperhomocysteinemia and hypercysteinemia in Portuguese type 2 diabetic patients with and without angopathy.

Methods
A population-based case–control study in 150 Portuguese type 2 diabetic patients was performed. The study population: group I – 75 patients with angiopathy and
Introduction
Adequate glycaemic, along with other cardiovascular risk factors control in type 2 Diabetes (T2D), and its beneficial impact on subclinical inflammation is associated with better microvascular outcomes.

Objective
To analyse the correlation between glycaemic control adequacy and systemic inflammatory markers, renal disease progression and cardiovascular risk factors.

Material and Methods
Retrospective cohort observational study of T2D patients (n=1900) with a minimum of 2 year follow up in the Endocrinology Department of Hospital de Egas Moniz from the year 2005 until 2014. Patients younger than 18 years of age and/or suffering from secondary diabetes were excluded. Fasting blood glucose and glycated hemoglobin variation were analysed and correlated with blood pressure control and renal function, systemic inflammatory and blood lipid profile markers. Descriptive statistical methods were employed: t-test student, ANOVA for continuous and chi-square for categorical variables.

Results
The patient sample had an average age of 61.2 years, being 59.7% female. A statistical significant relationship was documented between the glycaemic variation and renal disease progression (CKD-EPI P 0.045; spot urinary albumin P<0.001), lipid profile (non-HDL Cholesterol P<0.001) and inflammatory markers (CRP P 0.028; ESR P 0.01; Leucocyte count P 0.004).

Conclusions
Despite having the known limitations of a retrospective study, the sample size allowed the authors to document a possible association between glycaemic variation, renal disease progression, subclinical inflammation and blood lipid profile.

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EP541
Weight and weight variability correlates with subclinical inflammation and comorbidities in diabetes type 2: a retrospective study over the last decade
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Background
Management of obesity and overweight greatly improves glycemic control in type 2 diabetic (T2DM) patients and also provides positive impact in other cardiovascular risk factors in this population.

Objectives
Evaluate the impact of weight and weight variability in subclinical inflammation and comorbidities of T2DM patients, over the last decade.

Methods
Retrospective study of 1900 patients with T2DM, with a minimum of 2 years of follow-up and five evaluations at our Endocrinology outpatient clinic between 2005 and 2014. Patients under 18 years old, with secondary diabetes and BMI >40 kg/m2 were excluded. The weight variation was calculated using the S.D. of BMI for each patient with 11.0±2.0 determinations per patient over a mean follow-up of 7.25±1.1 years. The main outcomes of management selected included: BMI, blood pressure, lipid profile, renal function and systemic inflammatory markers. Descriptive statistical methods were applied, t-test and Pearson’s correlations where used to continuous variables and the χ² in categorical ones.

Results
The 1900 patients were aged 61.2±0.3 years at the first observation and 769 were men. There was a statistically significant relationship between BMI and BMI variability for systolic blood pressure (P<0.001 and P=0.036), BMI for diastolic blood pressure (P<0.001), creatinine (P=0.049), uric acid (P<0.001); albuminuria (P<0.01), triglycerides P<0.001, HbA1c (P<0.001), and non HDL cholesterol (P<0.015); monocytes (P=0.008).

Conclusions
This retrospective study has the inherent limitations. Allows an insight to the problem by the data volume. The BMI and its variability in this population was associated with elevation of chronic inflammatory markers (monocytes, creatinine and lipid panel. These data reinforce the importance of weight control in T2DM patients.

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EP540
Glycaemic variability and subclinical inflammation in type 2 diabetes: experience of a Portuguese centre in the last decade
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Introduction
Type IV Renal Tubular Acidosis (Type 4 RTA) is an underdiagnosed condition known to be more frequent in Diabetes Mellitus patients with moderate renal impairment. It is thought to be very common, with an incidence of 5.8% of hospital admissions in some series, being an increasing problem among the elderly and aggravated by polypharmacy.

Methods/Design
The authors describe 4 cases of Type 4 RTA associated with type 2 Diabetes diagnosed and followed in the Endocrinology department of Hospital de Egas Moniz.

Results
The population studied had an average age of 67 years, mean Diabetes duration of 8 years and all had arterial hypertension and hypercholesterolemia. All patients were on insulin therapy and had some degree of chronic renal disease. None of patients of group I with the genotypes Hp 2-1 or Hp 2-2 had a higher probability to have hyperhomocysteinemia (OR: 4.19; P=0.021) and hypercreatinemia (OR: 4.55; P=0.028) than diabetic patients from group II. The presence of 677TT and C677T genotypes in group I increased in five times (OR: 5.37; P=0.040) the probability to have hyperhomocysteinemia compared to group II. The association between haptoglobin and C677T polymorphisms increased the probability (OR: 4.14; P=0.004) of having hypercreatinemia in group I.

Conclusion
The haptoglobin and C677T of MTHFR polymorphisms are associated with a predisposition to hyperhomocysteinemia and can be considered genetic risk factors in angiopathy development of Caucasians type 2 diabetic patients.

Disclosure
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Subclinical hypothyroidism and features of metabolic syndrome in Saudi elderly women
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To investigate the frequency of subclinical hypothyroidism (SCH) in adults with metabolic syndrome (MetS). To assess whether MetS features were associated with SCH. Study subjects were recruited from consecutive patients attending outpatient clinics within the department of internal medicine at KAUH, Jeddah city, KSA. A case–control study was conducted among 122 elderly women. Each patient was matched with a control whose age did not differ by more than 2 years. Demographic and medical data were obtained. MetS was defined according to the American Heart Association. Continuous data are presented as means ± S.E.M. Differences between subjects with and without MetS were determined by Mann–Whitney’s U test and χ² tests where appropriate. Univariate relationships were estimated by Spearman’s correlation analysis. The level of significance was set at two-sided P values <0.05. The data were analysed using SPSS version 20.

The prevalence of SCH was 26% in the MetS group and 15% in the control group (P > 0.05). The prevalence of SCH increased with age (r = 0.241, P < 0.01). All obesity measures were consistently inversely associated with serum TSH level. Subjects with MetS had significantly higher levels of blood pressure, fasting blood glucose, fasting blood glucose profile (except for HDL-C which was significantly lower), and serum insulin than their control counterparts (P < 0.01). All anthropometric measurements and insulin resistance measures were lower in the control group than in MetS patients (P < 0.01). C-reactive protein was higher in the MetS patients than their matching controls (P < 0.01). SCH is increased in patients with MetS, therefore hypothyroidism should be considered in newly diagnosed MetS patients. Of all MetS components, waist circumference was the one that was negatively associated with serum TSH levels. Low-grade inflammation was more prevalent among the National Cholesterol Education Program-defined MetS patients than their age-matched controls.

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Controlling the obesity epidemic: where does the pharmacist weigh in?
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Background Obesity is a growing health concern in Albania. Obesity has been identified as a key risk factor for many chronic diseases including hypertension, dyslipidaemia and type 2 diabetes mellitus.

Methods It was used a descriptive cross-sectional study involved ten community pharmacies that were selected via stratified and systematic random sampling. A pretested self-administered questionnaire collected information on frequency and current level with obesity counselling, and the perceived effectiveness of four aspects of obesity management (diet and exercise, prescribed antiobesity medications, diet foods, and nonprescription products and dietary supplements).

Information on perceived confidence in achieving positive outcomes as a result of counselling and barriers to counselling was also collected. Descriptive and Spearman’s rank analysis were conducted using SPSS version 17. Responses with Likert scale rating 1(low score) to 5(high score) and binary choices (yes/no) were presented as mean (S.D.) and (95% CI), respectively.

Results The response rate was 83.6%. The overall mean (S.D.) responses indicated that pharmacists counselled obese patients sometimes to most of the time, 3.67 (1.19) and were neutral to comfortable with counselling about aspects of obesity management, 3.77 (1.19). Respondents perceived obesity management aspects to be somewhat effective, 3.80 (1.05). Of the four aspects of obesity management, diet and exercise, and diet foods were the highest ranked in terms of frequency of counselling, comfort level and perceived effectiveness. Pharmacists were neutral to comfortable in achieving positive outcomes as a result of obesity counselling (1.09). Overall mean responses of counselling obese patients by pharmacists were positively correlated with their perceived comfort with counselling and perceived effectiveness of obesity management aspects. The most anticipated barriers to obesity counselling were lack of patient awareness about pharmacists’ expertise in counselling and pharmacists’ opinions that obese patients lack willpower and are non-adherent to weight reduction interventions.

Conclusions Strengths, weaknesses and barriers related to obesity counselling by pharmacists in Albania were identified, and suggestions were provided to strengthen that role.

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showed the best significant correlation (\(r = 0.720\)) between the measured and calculated LDL-C by the ChenF. Regarding age, ChenF revealed more accurate results. For TG > 4.5 mmol/l (\(n = 957\)), LDL-C measured by direct assay was 3.12 ± 0.96 mmol/l (120.8 ± 37.0 mg/dl), by FF 3.07 ± 1.11 mmol/l (118.6 ± 42.8 mg/dl), ChenF 3.26 ± 1.14 mmol/l (126.2 ± 44.2 mg/dl), TsaiF 3.32 ± 1.13 mmol/l (128.3 ± 43.6 mg/dl) and DeLongF 3.20 ± 1.11 mmol/l (123.8 ± 43.1 mg/dl). Linear regression showed a significant (\(P < 0.001\)) better correlation (\(r = 0.947\), \(r^2 = 0.897\)) between the measured and calculated LDL-C by the ChenF.

Conclusions FF underestimated LDL-C and the other formulas overestimate it. For patients with TG < 4.5 mmol/l, ChenF provided more accurate for all studied groups. For TG > 4.5 mmol/l, TsaiF showed better correlation but regarding age ChenF revealed to be better for children and elderly and TsaiF for middle age patients. Our results suggest that TsaiF and ChenF may be more suitable for LDL-C estimation, even in the presence of moderate to severe hypertriglyceridaemia.

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**EP546**

**Glucose metabolism regulation in morbidly obese patients and in patients after biliopancreatic diversion**

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Introduction

Morbid obesity (MO) is associated with high frequency of type 2 diabetes mellitus (T2DM). Biliopancreatic diversion (BPD) is bariatric operation that results in rapid T2DM remission and increased GLP-1 levels. The aim of the study was to compare non-diabetic MO patients with normal weight controls and with patients who underwent BPD more than 2 years ago.

Methods

Blood glucose levels, IRI, GLP-1, GIP and glucagon were measured during the oral glucose tolerance test (OGTT) in three groups of patients. Patients of the 1st group (MO) had BMI > 40 (\(n = 22\)) and no history of diabetes mellitus. Patients after BPD were included in the 2nd group (\(n = 23\)), post-operative period median was 4.7 years (2.3–7.2). The 3rd group were normal weight controls (\(n = 22\)).

Results

Impaired glucose metabolism was revealed in 68.2% of MO patients (\(n = 10\)). In MO group fasting glucose, IRI and HOME-IR were maximal (\(P < 0.001\)). MO patients had higher fasting and stimulated GIP and glucagons levels. In the BPD group postprandial glucose (120 min) was lower, in 17.4% we found postprandial hypoglycemia (<2.8 mmol/l). Stimulated IRI concentration was significantly higher in the BPD group (\(P = 0.026\)). Fasting and stimulated GLP-1 were significantly higher in BPD (\(P = 0.037\) and \(P = 0.022\), respectively).

Conclusion

Hyperglucagonaemia, increased GIP levels and decreased GLP-1 levels are observed in MO. Glucose intolerance and insulin resistance incidence is higher in MO patients. Stimulated plasma IRI and GLP concentrations are significantly increased in BPD patients.

**Disclosure**

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**EP547**

**The relationship between the subclinical target organ damage and the levels of ischemia-modified albumin in hypertensive patients**

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**Aim**

To investigate the relationship between the presence of subclinical target organ damage (STOD) and the levels of ischemia-modified albumin (IMA) in hypertensive patients.

**Methods**

The study included a total of 106 patients, 53 with STOD and 53 without STOD. STOD was deemed present if fundus examination revealed a grade 3–4 retinopathy; the left ventricular mass index (LVMI) was >95 g/m² in females and >115 g/m² in males at echocardiography; carotid intimal media thickness (CIMT) was ≥0.9 mm; and 24-h urine had 30–300 mg albumin. IMA levels were assessed by spectrophotometric method using albumin cobalt binding test. All patients underwent ambulatory blood pressure monitoring (ABPM) for 24-h.

**Results**

The mean whole-day systolic blood pressure was higher in patients with STOD (128.19 ± 15.9 vs 118.55 ± 10.5, respectively \(P = 0.001\)). The mean diastolic blood pressure was similar in both of the groups (\(P > 0.05\)). The mean IMA level was higher in patients with STOD (0.63 ± 0.09 vs 0.53 ± 0.1 respectively \(P = 0.013\)).

**Conclusion**

Elevated IMA in patients with STOD is consistent with the role of ischemia and oxidative stress in development of target organ damage in hypertensive patients, and suggests that IMA can be used as an indicator to predict the presence of STOD.

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**EP548**

**The relationship between socioeconomic level, and the prevalence of masked hypertension and asymptomatic organ damage**

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**Background**

This study aimed to determine the prevalence of masked hypertension (MHT) and its association with asymptomatic organ damage (AOD) in a low socioeconomic district of Ankara, Turkey.

**Material and methods**

Data obtained from the medical records of 712 patients with no known diagnosis of hypertension that presented to a polyclinic due to symptoms related to elevated blood pressure (BP) and were screened for MHT were retrospectively reviewed. The essential hypertension (EHT) included 86 patients screened for AOD. The presence of AOD in patients diagnosed with MHT and the EHT group was recorded.

**Results**

Among the 712 patients, 206 were diagnosed with EHT and among the remaining 506 patients, 73 were diagnosed with MHT. The patients with MHT had a significantly higher left ventricular mass index, carotid intima media thickness, and 24-h urinary microalbuminuria level (all indicators of AOD) than those with EHT.

**Conclusion**

A significantly higher percentage of patients with MHT had AOD, as compared with those with EHT, in a low socioeconomic district of Ankara. Based on this
EP549
Management of hypoglycaemia after gastric bypass: a difficult challenge
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Introduction
Postprandial hypoglycaemia with hyperinsulinaemia after laparoscopic gastric bypass is an uncommon complication with an estimated prevalence of 0.2%. Its treatment includes acarbose, diazoxide, somatostatin and GLP-1 analogues or calcium channel blockers in case a strict diet does not work.

Case report
A 42-year-old woman with history of gastric bypass in 2005 due to severe obesity (preoperative weight 150 kg) attended our clinic 3 years after surgery reporting hypoglycaemic episodes occasionally accompanied by unconsciousness, occurring 3 h after food intake. The episodes resolved after sugar intake. ACTH stimulation test ruled out adrenal insufficiency. A 72-h fasting test was done with no pathological findings. A glucose tolerance test was also performed showing hyperglycaemia and hyperinsulinaemia. A CT scan of the abdomen did not find pancreatic nodules. Fractionated diet was started, followed by treatment with acarbose. Both measures were ineffective. Lanreotide treatment was subsequently administered with intolerance and no improvement. Diazoxide was titrated achieving only a partial response and the patient was referred to surgery for corporocaudal pancreatectomy in 2013. Pathological examination found diffuse nesidioblastosis. After the surgery, no hypoglycaemic episodes were observed. Moreover, the patient developed diabetes requiring treatment with insulin. One year after pancreatectomy the patient had a relapse of hypoglycaemia episodes even after insulin withdrawal. An overload test with mixed meal showed hyperinsulinaemic hypoglycaemia. Liraglutide 0.6 mg/24 h was prescribed but even after insulin withdrawal. An overload test with mixed meal showed hyperinsulinaemic hypoglycaemia. Liraglutide 0.6 mg/24 h was prescribed but even after insulin withdrawal. An overload test with mixed meal showed hyperinsulinaemic hypoglycaemia. Liraglutide 0.6 mg/24 h was prescribed but even after insulin withdrawal. An overload test with mixed meal showed hyperinsulinaemic hypoglycaemia. Liraglutide 0.6 mg/24 h was prescribed but even after insulin withdrawal. An overload test with mixed meal showed hyperinsulinaemic hypoglycaemia. Liraglutide 0.6 mg/24 h was prescribed but even after insulin withdrawal. 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Influence of normal food intake on the lipid profile of diabetic patients

Methods
A total of 248 diabetic patients were included (49.6% male; median age 57 years, range 40–79 years), recruited between April/2013 and August/2014 from the Outpatient Diabetes Education Program of Hospital de Santo António, Centro Hospitalar do Porto. Clinical and analytical evaluation took place in two moments (fasting = t₀, 2 h after a standard breakfast = t₁), with measurements of total cholesterol (TC), LDL cholesterol (LDL-C), HDL cholesterol (HDL-C) and triglycerides (TG). Paired LDL-C samples of patients with TG > 400 mg/dl and outliers (≥ 3 s.d. from the mean) were excluded from the analysis.

Results
TG concentration increased between the two moments (median difference t₁−t₀ = 6 mg/dl, P = 0.002) but the TC, LDL-C, HDL-C and non-HDL-C did not change significantly (P = 0.69; 0.75; 0.06 and 0.60, respectively). Performing an analysis according to the two therapeutic goals for LDL-C proposed by the ATP III, we found that the proportion of patients with LDL-C t₀ > 100 mg/dl and LDL-C t₁ > 100 mg/dl was 9.3% (5/54); and LDL-C t₀ ≥ 70 mg/dl and LDL-C t₁ < 70 mg/dl of 3.5% (1/29). Similarly, also a small percentage of patients with LDL-C t₀ < 100 mg/dl had values of LDL-C t₁ > 100 mg/dl (8.6%, 5/58). Considering the objective of 70 mg/dl, this percentage reached 14.3% (3/21).

Conclusion
The data presented question the need to fast for the determination of lipid profile. Further studies are needed to confirm these results and to demonstrate an association of postprandial lipid profile and cardiovascular risk in diabetic patients.

Disclosure
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Enzymes of the vitamin K cycle and progression of calcification in the vessel wall

Introduction
Renin-angiotensin-aldosterone system (RAAS) plays a significant role in the development of arterial hypertension (AH) in obese patient. Angiotensinogen expression in adipose tissue decreases during fasting and increases in case of overeating, that leads to changes in blood pressure (BP). The aim of the study was to assess the impact of obesity on the activity of RAAS and its role in the development of hypertension.

Methods
60 women, mean age 28.0 ± 2.1 years, BMI 37.7 ± 1.2 kg/m² participated in the study. Subjects were divided into groups depending of the AH presence: the 1st group consisted of 28 women with normal BP (systolic BP 115.6 ± 1.28 mm Hg; diastolic 81.0 ± 3.0 mm Hg). 32 women with AH (systolic BP 166.6 ± 5.4 mm Hg; diastolic BP 96.0 ± 3.2 mm Hg) were included in the 2nd group. 15 healthy normal weight women (19-25 years old, BMI 10.4 ± 2.3 kg/m²) were included in the control group. NaCl consumption not < 5 g/day was recommended to all patients. Plasma aldosterone concentration and renin activity were measured by radioimmunoassay with an automatic analyser («Immunotech», France). Blood samples were taken every 4 h during the day (8, 12, 16, 20, 24, 4 h) to evaluate the circadian rhythm of aldosterone secretion.

Results
In all obese patients plasma Na⁺ and K⁺ concentrations were normal. Urinary potassium excretion did not differ significantly from the control group (P > 0.05), sodium excretion was significantly decreased (P < 0.05). Both groups of obese patients have demonstrated low basal plasma renin activity compared with the control group (P < 0.001). Plasma renin activity values were not significantly different in the 1st and the 2nd groups (1st – 1.4 ± 0.06, 2nd – 1.15 ± 0.04 ng/ml per h, control group 2.18 ± 0.2 mg/ml per h). Morning aldosterone level was increased in the 1st group. At the same time, morning aldosterone level in the 2nd group was higher in comparison with the 1st group and with the control group (1st – 413.8 ± 20.6 pmol/l, 2nd – 664.1 ± 26.6 pmol/l; control group – 290.0 ± 19.6 pmol/l). Circadian rhythm of aldosterone in the control group was characterized by a maximum concentration in the morning hours (4–8 h) and lower concentration during the day, evening and night hours. A circadian rhythm of aldosterone in patients of the 1st group did not differ from the control group, while the 2nd group demonstrated an inversion of the circadian rhythm of aldosterone with maximum at midnight (24.00 h – 960.4 ± 140.7 pmol/l; 8.00 h – 597.6 ± 96.1 pmol/l, P < 0.005).

Conclusions
1. Plasma aldosterone concentration in the morning hours was elevated in the obese patients without hypertension.
2. Obese hypertensive patients had inverse aldosterone biorhythm with maximum at midnight.

Disclosure
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The functional parameters of renin-angiotensin-aldosterone system in obese patients

Introduction
Renin-angiotensin-aldosterone system (RAAS) plays a significant role in the development of arterial hypertension (AH) in obese patient. Angiotensinogen expression in adipose tissue decreases during fasting and increases in case of overeating, that leads to changes in blood pressure (BP). The aim of the study was to assess the impact of obesity on the activity of RAAS and its role in the development of hypertension.

Methods
60 women, mean age 28.0 ± 2.1 years, BMI 37.7 ± 1.2 kg/m² participated in the study. Subjects were divided into groups depending of the AH presence: the 1st group consisted of 28 women with normal BP (systolic BP 115.6 ± 1.28 mm Hg; diastolic 81.0 ± 3.0 mm Hg). 32 women with AH (systolic BP 166.6 ± 5.4 mm Hg; diastolic BP 96.0 ± 3.2 mm Hg) were included in the 2nd group. 15 healthy normal weight women (19-25 years old, BMI 10.4 ± 2.3 kg/m²) were included in the control group. NaCl consumption not < 5 g/day was recommended to all patients. Plasma aldosterone concentration and renin activity were measured by radioimmunoassay with an automatic analyser («Immunotech», France). Blood samples were taken every 4 h during the day (8, 12, 16, 20, 24, 4 h) to evaluate the circadian rhythm of aldosterone secretion.

Calcification is a physiological process in bone but occurs also pathologically in the vasculature, favouring cardio- and cerebrovascular diseases (CVD). Vitamin K metabolites, particularly K1 and MK-4, are associated with decreased vascular calcification especially in patients with chronic kidney disease. We investigated the expression of components of the vitamin K cycle (VKC) and the MK-4 synthesis (MKS) in aorta and bone of 26 brain dead organ donors in order to identify differences in the expression pattern during atherosclerosis (AS) stages in aortic vascular tissue and to compare these profiles in both tissue types. Gene expression was performed using TaqMan gene expression assays with a LC480 system. Determination of calcification stage was done histologically: 0 (unaffected vessels), 1 (intima thickening), 2 (intima calcification)). VKC enzymes VKOR, VKORL1, GGCX and the chaperone calu and the enzymes NQO1 and UBIAD1, necessary for MKS are both expressed in aortic and bone tissue. In the aorta, gene expression of VKOR, VKORL1, GGCX and the chaperone calu and the enzymes NQO1 and UBIAD1, necessary for MKS are both expressed in aortic and bone tissue. In the aorta, gene expression of VKOR, VKORL1, and calu differed significantly between the three atherosclerotic stages (P = 0.048; P = 0.023 and P = 0.038, respectively), whereas the expression of GGCX showed borderline significance (P = 0.060). In bone, gene expression of VKC and the MKS proteins did not differ in respective AS stages. Comparison of bone and aorta showed only significant differences in gene expression of calu, GGCX and NQO1 in the last stage of intima calcification. We are able to demonstrate that bone and aorta express the components of vitamin K cycle and of MK-4 synthesis. We also show the existence of a different gene expression pattern in AS progression in bone and aorta. These data might lead to a more comprehensive insight into the role of vitamin K metabolising enzymes in vascular calcification.

Disclosure
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Weight loss with bariatric surgery improves ischaemia modified albumin levels and oxidative status in morbidly obese patients
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Introduction
Oxidative stress is one of the possible mechanisms involved in the pathogenesis of the obesity-related metabolic complication. In this study, we aimed to investigate the effect of weight loss with bariatric surgery on IMa, a high sensitive C-reactive protein (hs-CRP), serum total antioxidant status (TAS), total oxidant status (TOS) levels.

Materials and methods
In this prospective study, plasma IMa, hs-CRP, TAS and TOS levels were measured before and 6 months after laparoscopic sleeve gastrectomy in 60 morbidly obese patients with a BMI of 46.6 ± 6.7 kg/m², 43 age-matched healthy subjects with a BMI of 24.6 ± 3 recruited as controls. Metabolic parameters including serum levels of fasting glucose, HbA1c, homeostatic model assessment of insulin resistance (HOMA-IR), C-peptide, LDL, HDL, triglyceride levels were also measured before and after surgery.

Results
Excess weight loss (EWL) and percentage of EWL were 34.9 ± 10.5 kg and 27.8% in obese patients. Plasma IMa levels before surgery were significantly increased in patients compared to controls (P < 0.05). We found significantly increased hs-CRP levels in patients compared to controls (P < 0.001). Plasma IMa and hs-CRP levels were significantly decreased in patients after 6 month of bariatric surgery (P < 0.05 and P < 0.001, respectively). At 6th month of surgery, BMI of patients was still significantly higher than controls (P < 0.01), hs-CRP levels were significantly increased in patients (P < 0.001) but there was no significant difference in IMa levels. A statistically significant reduction was found in the TAS values after the surgery (P < 0.001), but there were no significant changes in the TAS levels. Significantly decreased levels of fasting glucose (P < 0.01), HbA1c (P < 0.001), HOMA-IR (P < 0.01), C-peptide (P < 0.001), LDL-C (P < 0.001) and triglyceride (P < 0.001) and increased levels of HDL-C (P < 0.001) were observed after bariatric surgery.

Conclusion
Our findings supported that weight loss with bariatric surgery improves IMa, hs-CRP, TAS levels and metabolic profile in patients. Along with still higher BMI in patients after surgery, no significant difference in IMa levels between obese and healthy group suggested that bariatric surgery could have beneficial effects on oxidative stress beyond weight loss.

Disclosure
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Metformin treatment of hypothalamic obesity: the lesson of two cases
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Introduction
Hypothalamic obesity is defined as a syndrome of intractable weight gain as a result of hypothalamic lesions. Cramipharyngioma is responsible for more than half of the cases of hypothalamic obesity, but other pathologies can be implied. The syndrome can occur due to the tumour itself or its treatment (surgery or radiotherapy). Metformin is an antidiabetic drug that has also been used to treat nondiabetic obese patients, as it has been demonstrated to promote weight loss. Metformin alone has not been previously tested in patients with hypothalamic obesity.

Case presentation
We present the case of two patients with hypothalamic obesity, which were efficiently treated with metformin. The first case is a 44-year-old woman who has gained 45 kg following surgery for craniopharyngioma, despite caloric restriction and treatment with sibutramine and then orlistat. When she reached 150 kg, treatment with Metformin was initiated. During treatment she lost 34 kg in 30 months and her insulin resistance decreased significantly. The second case is a patient who was diagnosed at 6.4 years with a suprasellar mixed germ cell tumour (immature teratoma and germinoma). She underwent surgery, radiotherapy and chemotherapy. Following surgery, she developed severe hypothalamic obesity with insatiable bulimia, gaining dramatically 32 kg in 2.5 years. As complication of this major weight gain she had severe insulin resistance, dyslipidaemia, and steatohepatitis. As nutritional intervention and treatment with sibutramine and orlistat failed, treatment with metformin was initiated. After 1 year she lost 21 kg, her lipid profile and insulinemia improved considerably and her liver enzymes normalised.

Conclusion
Metformin proved to be an efficient and well tolerated treatment in these two patients with hypothalamic obesity, showing that it can be an option in these dramatic cases.

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Glycolysis in septic patients during early ICU hospitalisation shows differences vis-à-vis shock resolution
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Introduction
In glycolysis, glucose is converted into pyruvate. Patients with sepsis are prone to numerous metabolic alterations, including changes in carbohydrate metabolism. Aim To assess glucose metabolism in septic patients during the first day of ICU hospitalisation and evaluate this vis-à-vis shock resolution.

Subjects and methods
Ten patients with septic shock during the first day of ICU hospitalization were studied; measurements were done every 2 h in blood for glucose and in tissue (with microdialysis (MD) for pyruvate). Patients with diabetes were excluded. Six patients recovered from shock within 1–9 days. We analyzed the data on a cross-correlation matrix of 2-h' increments of blood glucose and MD pyruvate for patients with shock resolution and no shock resolution separately.

Results
In patients with shock resolution significant correlations were noted for blood glucose vs MD pyruvate (maximum r = +0.96, P = 0.004; with pyruvate lagging by 12 h); no significant correlations between blood glucose and MD pyruvate were measured in the patients with no shock resolution.

Discussion
During the first day of ICU hospitalisation septic shock patients who eventually resolved their shock status showed active glycolysis, whereas patients who remained in shock had early on no appreciable glycolysis.

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Renal hemodynamic status in patients with different classes of obesity
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Introduction and aims
Obesity is associated with increased single-nephron glomerular filtration rate, which may increase the risk of chronic kidney disease (CKD). Several biopsy studies showed the association between obesity and higher prevalence of CKD features, including segmental glomerulosclerosis, tubular atrophy, interstitial fibrosis, and arterial sclerosis. Another approach is to study intra-renal

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hemodynamics by ultrasound, where renal parenchymal damage in obesity may be reflected by intra-renal resistive indices.

Methods
We examined 108 patients with different classes of obesity (90 women and 18 men, mean age: 54.62±4.0 years). All patients were divided into three groups (III classes of obesity, divided by BMI). They underwent clinical and laboratory examination, which included lipogram, insulin, plasma homocysteine levels, microalbuminuria (MAU) in the morning urine. The result was determined directly, without any recalulation. UAI identified in excess of index higher than 20 mg/l. Study of intrarenal blood flow was performed by color Doppler with pulsed doplerometry on the device Aloka SSD-5500. We studied the main and intrarenal renal artery (segmental and interlobar) in the projection of the three segments of both kidneys. We determined the resistive characteristics of the arterial blood flow (RI and PI), calculated automatically by the standard formulas.

Results
The average level of insulin plasma and homocysteine exceeded the normal laboratory data in the III class – 31.57±0.41 mE/l (P<0.001) and 18.43±0.57 mE/l (P<0.001). The level of MAU exceeded in the II class – 20.44±0.46 mg/l (P<0.005) and III class – 53.09±7.87 mg/l (P<0.001). In the study of intrarenal blood flow RI and PI in the segmental and interlobar level of the arteries in this groups of patients were above normal values. In the segmental level: I class – RI = 0.64±0.01 (P<0.05) and PI = 0.99±0.2 (P<0.001); II class – RI = 0.71±0.01 (P<0.05) and PI = 1.24±0.03 (P<0.001); III class – RI = 0.70±0.01 (P<0.05) and PI = 1.33±0.04 (P<0.001). In the interlobar level: I class – RI = 0.63±0.01 (P<0.05) and PI = 0.99±0.2 (P<0.001); II class – RI = 0.70±0.01 (P<0.05) and PI = 1.24±0.03 (P<0.001); III class – RI = 0.68±0.01 (P<0.05) and PI = 1.31±0.04 (P<0.001).

Conclusions
These results suggest that obese patients have a sign of intravascular renal resistance and an increased risk for CKD.

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Influence of anthropometric parameters, leptin, adiponectin, and insulin resistance on blood pressure in obese women

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Relationship of body weight and blood pressure is very complex and still incompletely explained. Obesity, especially visceral, is one of the strongest predictors of arterial hypertension. Hypertension is six times higher in obese than in lean people, with its prevalence increases with an increase in BMI progressively. The mechanisms underlying hypertension in obese are not fully defined. The aim of this research was to determine the influence of various parameters on blood pressure and assume the possible pathogenetic mechanisms.

Materials and methods
The study included 90 obese women who were determined of average values of blood pressure, anthropometric parameters, levels of leptin, adiponectin, insulin levels, and HOMA-R index and established their mutual correlation.

Results
The mean values of blood pressure of patients was 146±15.68 mmHg for systolic and 92±10.83 mmHg for diastolic blood pressure. 33% of the subjects were normotensive. Correlation of anthropometric parameters and blood pressure values established their positive correlation, with a statistically significant impact of a waist circumference (P<0.001) and waist/ hip ratio (P<0.01). Insulinaemia and HOMA-R index correlated positively and significantly with the values of systolic and diastolic blood pressure (P<0.05). Levitin levels correlated positively and statistically significant with the systolic (P<0.001) and diastolic blood pressure (P<0.05). Correlations between adiponectin levels with the systolic and diastolic pressure are negative and not statistically significant. There is statistical significance of the negative correlation of adiponectin with fasting insulin levels and HOMA-R index.

Conclusion
Waist circumference, waist/hip ratio, insulin resistance, and leptin levels have statistically significant effect on blood pressure, and thus the occurrence of hypertension in obese women. Adiponectin through impact on insulin sensitivity probably contributes to the development of arterial hypertension.

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Galectin-3 and fibulin-1 in systolic heart failure patients with and without diabetes: relation to glucose metabolism and left ventricular contractile reserve

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Aims
Diabetic patients with heart failure (HF) have an adverse prognosis, which could be linked with reduced left ventricular (LV) contractile reserve. Galectin-3 (Gal-3) and fibulin-1 are potential biomarkers of fibrosis. The aims were to evaluate the impact of DM on Gal-3 and fibulin-1 levels and the association to LV contractile reserve in HF patients with and without diabetes (DM).

Methods and results
From an out-patient HF clinic 155 patients with systolic HF were included and underwent a low-dose dutamidine echocardiography and blood sampling for analyses of plasma Gal-3 and fibulin levels. Oral glucose tolerance test (OGTT) was performed in non-diabetic HF patients. Based on history of DM and OGTT patients were divided into normal glucose tolerance (NGT) (n=95), impaired glucose tolerance (IGT) (n=25), and DM (n=60).

Results
Galactin-3 levels were 17.9 mg/ml in diabetics (P<0.02) while fibulin-1 levels were not influenced by DM status. Gal-3 was associated with LV contractile reserve in a univariable regression model; standardized β (s.e.m.) (β = 0.19, P = 0.03), but not in a multivariable model including eGFR, (β = 0.04, P = 0.66). Fibulin-1 was not associated with LV contractile reserve in a univariable model (β = −0.06, P = 0.51). HbA1c was independently associated with Gal-3 (β = 0.16, P = 0.02) and fibulin-1 (β = 0.16, P = 0.04) in a multi-variable regression model including eGFR.

Conclusion
Gal-3 and fibulin-1 levels were elevated in diabetic HF patients, associated with HbA1c, but not with LV contractile reserve.

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EP561

The effect of the type of the bariatric surgery in the lipid profile: an age, sex, BMI, and excess weight loss matched study

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Introduction
Bariatric surgery improves lipid profile. A still unanswered question is whether this improvement is merely weight dependent or also results from factors inherent to specificities of the bariatric procedure itself. We aimed to study lipid profile 1 year after bariatric surgery and compare its changes between the different procedures in patients matched for initial weight and for weight loss.

Methods
We retrospectively analysed patients submitted Roux-en-Y gastric bypass (RYGB), adjustable gastric banding (AGB), or sleeve gastrectomy (SG) between 2010 and 2013. Patients were matched for age (±5 years), sex, pre-surgery BMI (±2 kg/m²), and EWL (±5%). Baseline and 1-year lipid profile, its variation and percentage of variation was compared between surgeries.

Results
We analysed 229 patients: 72 pairs RYGB-AGB; 47 pairs RYGB-SG; and 33 pairs AGB-SG. The median age was 41 (35–52) years and 11.8% were males. BMI at the time of surgery was 48.0±4.0 and 32.1±4.4 kg/m² at 1 year. EWL at 1 year was 64.2±18.9%. There were no differences in baseline lipid profile between patients submitted to different types of bariatric surgery. At 1 year, LDL
and TG improved similarly with all surgeries. TC and LDL at 1 year decreased significantly more in patients submitted to RYGB than in weight-matched patients undergoing AGB or SG.

Conclusions
RYGB is the only bariatric surgery that reduces TC and LDL in age-, sex-, BMI-, and EWL-matched patients. All three procedures improved TG and HDL similarly when the confounding effect of weight loss is eliminated.

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**EP562**

Comparison of demographic and biochemical characteristics among younger and older patients with metabolic syndrome

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**Aims**
The metabolic syndrome (MetS) is a summary measure of important CVD risk factors that frequently coexist. The syndrome is evident in 20–30% of middle-aged women and has been linked to the development of CVD and diabetes. The aim of the study was to examine the differences in demographic and biochemical profiles among older (≥60 years) and younger (<60 years) patients with MetS.

**Methods**
The study was included 45 older (mean age 63.1 ± 12.1 years, 25 females and 20 males) and 40 younger (mean age 42.3 ± 9.9 years, 30 females and 10 males) patients with MetS. MetS was defined as in ATP III. Demographic and biochemical parameters were compared between groups. Insulin resistance (IR) was estimated using the homeostasis model assessment (HOMA).

**Results**
Among older patients, 11.9% were smokers and 9.1% informed alcohol consumption. However, 29.5% of younger patients were smokers and only 12.1% of them consumed alcohol (P = 0.05 and P = 0.30). Mean levels of waist circumference, systolic, diastolic blood pressures, triglyceride, and LDL-cholesterol were statistically significantly higher than those of younger patients with MetS (P = 0.001, P = 0.01, P = 0.001, P = 0.02, and P = 0.002 respectively). Mean levels of HOMA-IR were found to be 2.3 ± 0.9 in young and 2.7 ± 0.02 in elderly group.

**Conclusions**
There are differences between older and young patients with metabolic syndrome for waist circumference, smoking, blood pressures, and lipid levels.

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**EP563**

The risk of future IRS among women with history of gestational diabetes

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**Background and aims**
The history of GDM predisposes to cardiovascular disease (CVD) in the future. The aim of this study was to evaluate risk factors predicting the development of glucose intolerance and insulin resistance syndrome (IRS) in women with history of GDM in the future.

**Materials and methods**
55 women who had GDM ≥12 years before were enrolled into the study. After clinical examination 75 g OGTT and inflammatory markers (hsCRP, uric acid, interleukin 6 (IL6), tumor necrosis factor alpha (TNFα), visfatin, plasminogen activated inhibitor 1 (PAI1), asymmetric dimethylarginine (ADMA), and adiponectin) was performed to evaluate of current metabolic status after a 3-year follow-up period. Based on IDF criteria participants were classified into two groups as normal (group 1) and IRS (group 2). We evaluated the relationship between metabolic status and complete risk factors such as: age, BMI, family history of DM, poor obstetric history, HbA1c and OGTT glucose levels at diagnosis of GDM; weight gain and insulin requirement during index pregnancy.

**SPSS 21 was used to analyse data.**

Results
51% of participants developed IRS after 10th year of delivery. No predictive factor was found except screening time, first hour glucose level at the diagnosis of GDM and insulin requirement during index pregnancy. Although difference was not significantly, patients in group 2 were found to have higher BMI, much more family history of DM before pregnancy and also they put less excess weight during pregnancy. As compared inflammatory parameters between two groups; HOMA-IR, hsCRP, visfatin, IL6, and PAI1 levels were detected statistically higher; on contrary adiponectin level was less in group 2 than group 1. And currently, 43% of all participants were found that they had at any level glucose intolerance and higher insulin levels at basal and first hour of OGTT.

**Conclusion**
Early screening of GDM and following the patient during gestational period is important but it’s much more important to follow those individuals who had high BMI, family history of DM and high glucose at first hour of OGTT at the beginning; they should be monitored closely postpartum and at least yearly follow-up should be done based on increased risk for developing IRS and therefore CVD.

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**EP564**

Haematopoietic system 3 years after gastric bypass

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Bariatric surgery, especially malabsorptive procedures like gastric bypass, can lead to anemia due to lack of iron absorption as well as vitamins essential for the normal functioning of the hematopoietic system.

**Methods**
We have analysed changes in red blood cells (RBC), haemoglobin (Hb), white blood cells (WBC), serum iron (Fe), and vitamin B12 3 years after gastric bypass in 142 morbidly obese patients (female, n = 108 and male, n = 34). All patients were on oral supplementation with 100 mg of iron and 200–400 mg of folic acid after surgery as well as 2500 μg of OHB12, i.m. injections every 3 months.

**Results**
Before surgery average BMI was 43.9 kg/m2 and 3 years after BMI was 30.5 kg/m2 (P < 0.001). Change in number of RBC was nonsignificant (4.65 ± 5.9 vs 4.42 ± 1.22 × 1012/l; P > 0.05) before and after surgery. There was no difference in Hb concentration between two measurements (137.9 ± 15.5 g/l vs 128.9 ± 16.3 g/l; P > 0.05). Number of WBC was lower after surgery (10.7 ± 3.2 × 109/l vs 5.7 ± 1.3 × 109/l) with significance: P > 0.001, but among reference range. Serum iron level increased after surgery but that was not significant (11.4 ± 1.3 μmol/l vs 13.0 ± 1.8 μmol/l; P > 0.05). Vitamin B12 level remained within normal range 3 years after gastric bypass (922.5 ± 212.2 pmol/l vs 866.7 ± 201.1 pmol/l; P > 0.05) without difference.

**Conclusion**
Even gastric bypass as malabsorptive bariatric procedure, can lead to anemia, adequate supplementation of iron, folic acid and vitamin B12, after surgery, may prevent anemia and vitamins essential for haematopoietic system deficiency during 3 years follow-up period.

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**EP565**

Patients with acute coronary syndrome have lower testosterone then healthy controls

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**Objective**
Several studies report the association of low testosterone with ischaemic heart disease although the results are inconsistent. In our study we tried to evaluate the relationship between sex hormones and incidence of acute coronary syndrome (ACS).

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Methods
This was a cross-sectional study. In 111 subjects (69 patients with ACS and 42 age-matched controls) we measured total testosterone, estradiol, SHBG, FSH, and LH by electrochemiluminescence and calculate free androgen index (FAI). Patients with cancer, antiandrogen or testosterone treatment were excluded. In all patients we examined risk factors of myocardial infarction (hypertension, diabetes mellitus, dyslipidaemia, smoking, waist circumference, and BMI). Results were correlated by unpaired T-test and linear regression in SPSS system. In all subjects quartile analysis according to testosterone levels was performed.

Results
Patients with ACS have lower total testosterone levels comparing with controls (12.37 nmol/l vs 15.66 nmol/l, P = 0.009). Patients had also lower levels of FAI and higher levels of FSH and LH but these were not significant. There was no difference in estradiol levels between the groups. In linear regression model testosterone correlated with waist circumference (R² = 0.082, P = 0.002) and weight (R² = 0.076, P = 0.002). In quartile testosterone analysis patients with testosterone levels in the lowest quartile had significantly higher incidence of ACS comparing with patients in the highest quartile (RR 1.72, CI 1.1; 2.6). Patients in the lowest testosterone quartile had also higher incidence of diabetes mellitus, dyslipidaemia, hypertension, and smoking.

Conclusions
Patients with ACS have significantly lower total testosterone levels and inversely, patients in the lowest testosterone quartile have higher incidence of ACS. Testosterone level correlates significantly with weight and waist circumference. Low testosterone is strongly associated with adiposity in patients with ACS and probably plays a role in metabolic syndrome.

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HLA and metabolic parameters that define obesity in Amerindians for the first time
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Metabolic syndrome and obesity are principal causes of morbidity all over the world, particularly for their association to cardiovascular risk. There is now an obesity worldwide epidemic (Globesity). Amerindians are often living in countries and remote areas with unavailable sophisticated diagnoses methodologies. However, waist circumference is a reliable and easy to record parameter of visceral obesity and MS. Waist circumference normal values are not yet established in Amerindians: South Asian and Japanese values have been recommended for Amerindian use. The purpose of this study is to objectively determine for the first time the waist circumference measure cut-off points for Amerindians, by using i) HLA phenotype to ensure that population tested is Amerindian and ii) measurement of biochemical markers which were diet independent. A total of 303 unrelated Amerindian adults recently immigrated to Madrid were studied; they were healthy, since they were questioned and tested as appropriate for blood donation and recent weight increase. Waist circumference was measured in these voluntary blood donors after written consent. Chosen subjects for study had HLA quasi-specific Amerindian genes. Amerindians with type 1 or 2 diabetes or family antecedents were removed from the study. A receiver operating characteristic analysis was used to compare the predictive validity and to find out the optimal cut-off points of waist circumference normal values. Cut-off points were ≤88.5 cm in males and ≤82.5 cm in females. Obtained waist circumference values recorded here in normal Amerindians are different to the previously recommended ones: those of South Asians. In addition, PPARγ and adiponectin gene linkage to obesity Amerindians was not observed. These parameters may be of great value for Spain and American countries for establishing preventive programs in order to predict and control metabolic syndrome.

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Does the presence of obesity and/or metabolic syndrome affect the course of acute pancreatitis?
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Objective
The incidence of acute pancreatitis (AP) is rising with increased prevalence of obesity, which exacerbates pancreatic injury. Metabolic syndrome (MS) is defined as a cluster condition of cardiovascular risk factors, including hyperglycaemia, dyslipidaemia, hypertension, and central obesity. We analysed if the presence of obesity and/or MS affects the course of pancreatitis.

Methods
Data were collected from 140 patients with AP between January 2010 and February 2013. Anthropometric data, including BMI and waist circumference, were measured. Biochemical tests were used including fasting glucose, triglyceride, LDL and HDL cholesterol levels, and total cholesterol level. Atlanta criteria, Acute Physiology and Chronic Health Evaluation II, and Ranson scoring system were used to define severe AP. Patients were classified as having MS based on the International Diabetic Federation criteria.

Results
The mean BMI was 30.15 kg/m². Sixteen (11.4%) patients had severe AP, whereas 124 (88.6%) patients had mild AP. We found that 62.8% of patients with AP fulfilled the criteria of MS (P = 0.000). Body weight can be used to predict clinical severity of AP with significant P value = 0.009.

Conclusions
The presence of MS in patients with pancreatitis is noticeable, but it does not affect the course of disease severity, whereas obesity correlates with pancreatitis severity.

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Gender-related risk of cardiovascular diseases in patients with type 2 diabetes mellitus
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Introduction
The main causes of death in the world today is non-communicable diseases (NCDs). A research of the World Bank found out that 82% of deaths in Ukraine are caused by chronic NCDs, 3.6% of which compose diabetes mellitus. And since the course of type 2 diabetes mellitus (T2DM) is usually long, it requires special, costly medical care for significant period of patient’s lifetime.

Materials and results
Our research involved 592 males and 1170 females with T2DM. We determined BMI, glycæmia, total cholesterol, HDL-C, and non-HDL-C. Dyslipidaemia is established with cholesterolaemia over 5.20 mmol/l and with HDL-C under 1.02 mmol/l in males and under 1.29 mmol/l in females. In our study group, cholesterol level in men was 6.41 ± 0.03 mmol/l in women – 6.23 ± 0.01 mmol/l (P < 0.05), while HDL-C was respectively 1.89 ± 0.88 and 1.88 ± 0.07 mmol/l (P < 0.05), and non-HDL-C – 4.60 ± 0.02 and 3.38 ± 0.05 mmol/l (P < 0.05).

Patients were divided, according to cholesterolaemia, into the following groups: under 5.3, 5.3–6.5, and over 6.5 mmol/l. In relation to this, males were the following percentages: 38, 57, and 5%; females: 28, 64, and 8%. Regarding fasting glycæmia, patients’ groups were: under 6.2, 6.2–7.8, and over 7.8 mmol/l. According to BMI we had the following classification: normal weight, overweight, obesity. And male patients’ cholesterol was respectively as follows: 5.81 ± 0.03, 6.56 ± 0.03, and 7.50 ± 0.03 mmol/l.

Conclusions
i) Atherogenic dyslipidaemia in 70% of patients with T2DM of both sexes is caused by an increase in blood non-HDL-C. ii) Atherogenic dyslipidaemia correlated with the state of compensation of diabetes and body weight. iii) Therapeutic correction of dyslipidaemia in patients with T2DM should be normalization of blood glucose and body weight.

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Effect of obesity and diabetes mellitus type 2 on vascular stiffness
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Aim
To investigate the impact of overall obesity (Ob) and diabetes mellitus type 2 (DM2) on arterial stiffness and degree of insulin resistance in patients with arterial hypertension (AH) and abdominal Ob (AOb).

Design and methods
74 subjects were divided according to presence of AH, AOb, Ob, and DM2 without insulin therapy. Control group 1 consisted of 26 subjects without AH, AOb, Ob, and DM2. All patients with AH were also diagnosed with AOb and amounted to 48 subjects. Then patients with AH and AOb were divided into two groups (groups 2 and 3 respectively) according to presence of Ob, defined by BMI and furthermore, DM2. Carotid- femoral pulse wave velocity (PWVc-f) measurements were performed using SphygmoCor. Homeostasis model assessment-insulin resistance (HOMA-IR) was calculated by the following formula: fasting plasma insulin (mU/ml) × fasting plasma glucose (mmol/l)/22.5.

Results
In the group comparison by BMI: PWVc-f and HOMA-IR increased consistently from groups 1 to 3. PWVc-f and HOMA-IR increased consistently from groups 1 to 3. PWVc-f and HOMA-IR were significantly higher in hypertensive patients with AOb and DM2 than in hypertensive patients with AOb and without Ob (PWVc-f = 8.69 ± 1.8 and PWVc-f = 7.43 ± 1.3; P < 0.05). HOMA-IR did not show significance. In the group comparison by presence of DM2: PWVc-f and HOMA-IR were significantly higher in hypertensive patients with AOb and DM2 than in hypertensive patients with AOb and without DM2 (PWVc-f = 9.5 ± 1.8 and PWVc-f = 7.71 ± 1.5; P < 0.001). Significant differences among groups persisted after adjustment for age, sex, and BMI.

Conclusions
The presence of overall Ob together with AOb had a significant adverse effect on arterial stiffness in patients with AH both men and women. This adverse effect is similarly present in patients with AOb. Measurement of PWVc-f showed higher significance vs HOMA-IR measurements in the study groups.

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EP570
Metabolism of sphingolipids in experimental obesity and insulin resistance
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Sphingolipids constitute the structural base for all types of biological membranes, and are numerous in human and animal tissues. Metabolites of sphingolipids act as biological effectors, modulators and mediators in a number of biochemical processes. They are known to be pathogenic in various human pathologies.

We aimed at studying activity of sphingomyelinase, concentrations of sphingomyelin and its metabolites, such as ceramides and sphingosine, in organs of rats with experimental diabetes.

Experimental model of obesity and insulin resistance was used to study activity of sphingomyelinase, and concentrations of sphingosine and ceramide. As compared with the controls, in the liver of experimental animals activity of neutral and acid sphingomyelinase was found to increase by 25 and 21% respectively. In skeletal muscles of obese animals, activity of neutral and acid sphingomyelinase increased by 45 and 70% respectively. The findings can be the evidence for stimulation of sphingomyelinase activity in the liver and skeletal muscles in rats with experimental obesity. Significant alterations in the content of sphingomyelin and its metabolites were observed in obese rats; these alterations were found to be oppositely directed. In the liver of obese rats, sphingomyelin was found to decrease by 25%; while in skeletal muscles its concentration decreased more than by 31%. Concentrations of ceramide and sphingosine in the liver of obese rats were found to increase by 15 and 23%, respectively, as compared with the controls. In skeletal muscle of obese rats, concentrations of ceramide and sphingosine increased by 19 and 68% respectively.

We have established increase in the activity of sphingomyelinase and accumulation of ceramide and sphingosine, metabolites of sphingomyelin, in the liver and skeletal muscles of rats with experimental obesity and insulin resistance. Ceramide overproduction plays a key role in the onset and development of insulin resistance.

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EP571
Adiponectin response to vegetarian diet is gender-dependent and inversely related to uric acid
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Introduction
Beneficial influence of vegetarian dietary habits in reducing common risk factors of metabolic syndrome has been recently evidenced. However, adiponectin production and secretion has been scarcely studied in vegetarians, despite its important potential in recovering metabolic homeostasis by reducing inflammation and insulin resistance.

The aim of this study was to evaluate the influence of vegetarian diet on serum adiponectin levels and its association to the established inflammatory and metabolic biomarkers.

Methods/design
Total serum adiponectin (ADN), leukocytes (L), CRP, plasma glucose (PG), insulin (INS), and uric acid (UA) were measured in healthy, non-obese, age-matched vegetarian (n = 40; M/F = 16/24) and omnivore subjects (n = 39; M/F = 15/24). HOMA-2 model was used for the assessment of β-cell function (BS), insulin sensitivity (IS), and insulin resistance index (IRI).

Results
Serum ADN levels were significantly higher in female vegetarians than the respective omnivore controls (14.2 ± 5.82 mg/ml vs 10.82 ± 3.29 mg/ml; P = 0.017), whereas no dietary-associated difference was observed in male vegetarian and omnivore subjects respectively (6.87 ± 2.57 mg/ml vs 6.74 ± 1.07 mg/ml; P = 0.898). Stepwise multiple regression analysis identified uric acid as the significant negative determinant of ADN in vegetarians (b = −0.4585, P = 0.002), while in omnivore subjects only BMI was found to be significantly associated to ADN levels (b = −0.4439, P = 0.016). In comparison to controls, significantly lower INS (47.6 ± 19.2 pmol/l vs 57.7 ± 23.7 pmol/l; P = 0.042) and IRI (1.01 ± 0.42 vs 1.22 ± 0.49; P = 0.041), as well as higher BS (115.5 ± 42.9% vs 94.2 ± 35.3%; P = 0.019) were found in vegetarians.

Conclusion
Vegetarian dietary habits result into improved insulin sensitivity and β-cell function. Gender diversity in adiponectin response and inverse association to uric acid indicate distinct effects of vegetarian diet to adipose tissue metabolism.

Disclosure
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EP572
Fibrate therapy predispose to influenza vaccine-induced rhabdomyolysis
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Introduction
Fibrates are widely used to manage dyslipidemia but these drugs can induce rhabdomyolysis with acute renal failure. Rhabdomyolysis is a skeletal muscle cell damage condition associated with the release of toxic components of the cells and to the end renal failure. The onset of rhabdomyolysis can extend to 6 months with fibrate therapy. Some researchers propose that the influenza vaccine can induce the rhabdomyolysis in patients who receive myotoxic drugs. Here we present a case who develops rhabdomyolysis and acute renal failure after influenza vaccine during fibrate therapy.

Case
A 65-year-old male patient admitted to the hospital with weakness and pain of the extremity muscles. He had tenderness widespread of the body and feel difficulty to move. He had coronary heart disease and hyperlipidemia. He was taking 267 mg of fenofibrate daily for 5 months and had influenza vaccine administration a week before admission to the hospital. Laboratory examination showed markedly elevated serum creatine kinase levels (27 730 U/l) and creatinine was...
Outcomes of gastric bypass for morbid obesity after 5-year follow-up
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Introduction
Currently, there are few data on long-term effects of bariatric surgery. We present the results of 5-year follow-up of a cohort of patients with gastric bypass surgery (GBP).

Objectives
i) To determine the prevalence of major comorbidities of morbid obese; ii) to evaluate the gastric bypass effect on this comorbidities, and 10-year estimated cardiovascular risk after 5-year follow-up; and iii) to assess the impact of bariatric surgery on the quality of life in these patients.

Methods
Prospective analysis in a cohort of 124 patients with morbid obesity who underwent bypass surgery. Demographic and anthropometric parameters, 10-year risk for coronary heart disease (estimated by Framingham risk score), complications from surgery and quality of life through Bariatric Analysis and Reporting Outcome System (BAROS) test were analysed before surgery and during follow-up.

Results
A total of 124 patients, who underwent surgery between 2005 and 2009, where included. The mean age was 37.8±10.29 years, 76.6% were women and the mean preoperative BMI was 51.71±7.35 kg/m². At 2 and 5 years of follow-up, remains a BMI of 30.48±4.7 and 31.27±7.08 kg/m² respectively. After 5 years of follow up, the percentage of weight lost was 68.31%. Remission of hypertension, dyslipidemia, and diabetes mellitus type 2 had occurred in 89.5, 95.8, and 95.7% respectively (P<0.001). Average weight gain was 8.1 kg. At admission, 24 (31.6%) patients were overweight and 35 (46.0%) were obese; at TOS, 9 (11.8%) were overweight and 57 (75%) were obese (P<0.001). Twenty-nine (37.2%) patients met the criteria for MetS at admission, 44 (56.6%) at TOS (the additional 15 met the criteria solely due to weight gain). Three had diabetes at admission, 12 (15.8%) at TOS (P=0.012).

Conclusions
We conclude that obesity and MetS are highly prevalent in our centre. Given that obesity is a significant contributor to MetS and its complications, patients in forensic institutions such as this should receive appropriate weight management programme from time of admission. Urgent investment in dietetic and physiotherapy service is needed.

Can obese patients on antipsychotic medications achieve weight loss in an unmodified general population lifestyle-intervention weight management programme
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Introduction
Many antipsychotics are obesogenic and contribute to significant weight gain with serious implications on patients’ physical and mental well-being. However, patients on antipsychotics are often excluded from unmodified lifestyle-intervention weight management programmes and trials.

Objectives
To determine if weight loss is possible for antipsychotic-medicated obese patients when enrolled in an unmodified lifestyle-intervention weight management programme.

Methods
Data from 44 antipsychotic-medicated participants (AP) and 88 matched control participants (CP) were analysed to determine weight outcomes. Dietary and activity behaviours at baseline for an AP sub-cohort were also reported. Results were expressed as mean (95% CI); Mann-Whitney U test was used to assess differences between cohorts.

Results
Enrolment mean weight of AP was 139.8 kg (130.5–149.0 kg) compared with CP of 140.5 kg (134.4–146.6 kg; P=0.478). Enrolment BMI was 49.1 kg/m² (46.0–52.3) compared with 48.9 kg/m² (46.8–51.1; P=0.515). Twenty-five AP participants lost weight (mean weight loss: −9.1 kg). There was no difference in weight outcomes in AP compared to CP groups (−2.0 vs −2.4 kg; P=0.824). Also 9 (20.5%) AP participants lost 5% baseline weight compared with 18 (20.5%) in CP (P=0.99) while 5 (11.4%) in AP lost 10% weight compared with 6 (6.8%) in CP (P=0.373). At baseline, the AP group ate fast food 1.7±1.2 times/week, fresh fruit 1.0±1.4 times/day and reported 2.5±3.0 missed breakfasts/week. Baseline gait speed was lower in AP group (0.99±0.2 m/s vs 1.09±0.34 m/s in CP cohort) and improved slightly to 1.01±0.3 m/s.

Conclusion
Modest weight loss can be achieved in patients on long-term antipsychotics enrolled into an unmodified weight management programme designed for the general population. Typical dietary strategies such as encouraging breakfast restrictions on freedom and poor motivation to healthy lifestyle and physical activities.

Aim
To establish the prevalence of obesity and metabolic syndrome (MetS) in a secure forensic psychiatric hospital in the Republic of Ireland (ROI).

Methods
We carried out a longitudinal study in the National Forensic Mental Health Service in the (institution name, four words), Dublin, National Choleseterol Educational Program, Adult Treatment Panel III (NCEP/ATP III) definition was used to diagnose MetS.

Results
Number of patients was 76 (males = 68 (89.5%)). Mean age was 44.7 years (S.D. = 13.4). All patients were on long-term antipsychotics. Duration of admission was longer in males (9.6 years (S.D. = 10.5) vs 3.8 (S.D. = 2.9) in females, P=0.1232), mean was 9.2 (S.D. = 10.2). Mean weight at admission was 90.2 kg (S.D. = 17.7), BMI = 30.0 kg/m² (S.D. = 5.9); this increased at time of study (TOS) to 98.3 kg (S.D. = 17.9), P=0.006, BMI = 32.8 (S.D. = 6.1, P<0.001). Average weight gain was 8.1 kg. At admission, 24 (31.6%) patients were overweight and 35 (46.0%) were obese; at TOS, 9 (11.8%) were overweight and 57 (75%) were obese (P<0.001). Twenty-nine (37.2%) patients met the criteria for MetS at admission, 44 (56.6%) at TOS (the additional 15 met the criteria solely due to weight gain). Three had diabetes at admission, 12 (15.8%) at TOS (P=0.012).

Conclusion
We conclude that obesity and MetS are highly prevalent in our centre. Given that obesity is a significant contributor to MetS and its complications, patients in forensic institutions such as this should receive appropriate weight management programme from time of admission. Urgent investment in dietetic and physiotherapy service is needed.

Outcomes of gastric bypass for morbid obesity after 5-year follow-up
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Introduction
Patients in secure forensic psychiatric units are at high risk of developing obesity due to complex interplay of factors including antipsychotic medications, poor motivation to healthy lifestyle and physical activities.

Aim
To establish the prevalence of obesity and metabolic syndrome (MetS) in a secure forensic psychiatric hospital in the Republic of Ireland (ROI).

Methods
We carried out a longitudinal study in the National Forensic Mental Health Service in the (institution name, four words), Dublin, National Choleseterol Educational Program, Adult Treatment Panel III (NCEP/ATP III) definition was used to diagnose MetS.

Results
Number of patients was 76 (males = 68 (89.5%)). Mean age was 44.7 years (S.D. = 13.4). All patients were on long-term antipsychotics. Duration of admission was longer in males (9.6 years (S.D. = 10.5) vs 3.8 (S.D. = 2.9) in females, P=0.1232), mean was 9.2 (S.D. = 10.2). Mean weight at admission was 90.2 kg (S.D. = 17.7), BMI = 30.0 kg/m² (S.D. = 5.9); this increased at time of study (TOS) to 98.3 kg (S.D. = 17.9), P=0.006, BMI = 32.8 (S.D. = 6.1, P<0.001). Average weight gain was 8.1 kg. At admission, 24 (31.6%) patients were overweight and 35 (46.0%) were obese; at TOS, 9 (11.8%) were overweight and 57 (75%) were obese (P<0.001). Twenty-nine (37.2%) patients met the criteria for MetS at admission, 44 (56.6%) at TOS (the additional 15 met the criteria solely due to weight gain). Three had diabetes at admission, 12 (15.8%) at TOS (P=0.012).

Conclusion
We conclude that obesity and MetS are highly prevalent in our centre. Given that obesity is a significant contributor to MetS and its complications, patients in forensic institutions such as this should receive appropriate weight management programme from time of admission. Urgent investment in dietetic and physiotherapy service is needed.

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consumption and reducing fast food and increased physical activities are relevant to this cohort of patients.

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EP576
Factors affecting gender differences in the association between health-related quality of life and metabolic syndrome components: Tehran Lipid and Glucose Study (TLGS)
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Introduction
Gender differences in the association between health-related quality of life (HRQoL) and metabolic syndrome (MetS) have been studied by previous researches. This study aimed to assess influential factors causing gender differences between HRQoL and MetS components using structural equation modelling.

Methods
A sample of 950 adults from TLGS were recruited in this study between 2005 and 2007. Health-related quality of life was assessed using the Iranian version of SF-36. Structural equation modelling was applied to determine the relationships between the constructs of MetS components (MetScs) and HRQoL within the gender groups.

Results
Based on the primary hypothesis, MetScs, physical and mental HRQoL were fitted in a model ($\chi^2$df = 1.52, RMSEA = 0.023, CFI = 0.99, and GFI = 0.97). The adjusted negative effect of MetScs on physical HRQoL was significant only in women. The proportion of all the cardio-metabolic risk factors as well as physical domain subscales were higher in women ($P < 0.05$). Among socio-behavioural factors, physical activity in both men ($\beta = 3.19$, $P < 0.05$) and women ($\beta = 3.94$, $P < 0.05$), age ($\beta = -3.28$, $P < 0.05$) and education ($\beta = 2.68$, $P < 0.05$) just in women and smoking had a sex-specific indirect effect on the association between physical HRQoL and MetScs, none of the socio-behavioural factors was found to have a direct effect on this association between men and women significantly.

Conclusion
Structural differences of physical HRQoL and MetScs as well as different influential patterns of socio-behavioural factors specifically age and smoking seems to have a pivotal role to create this gender differences. Although, the proportion of SBP, WC and bodily pain were the highest in both genders, except for DBP, all the cardio-metabolic risk factors and physical subscales had significant higher proportion in women.

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EP578
A 5-year review of the metabolic changes after laparoscopic sleeve gastrectomy among obese Hong Kong Chinese in a regional hospital Cheuk Wah Ho, Grace Kam & Man Wo Tsang
United Christian Hospital, Hong Kong, China.

Background and aims
Obesity is a global problem. Laparoscopic sleeve gastrectomy (LSG) was introduced in our hospital since 2008. This study aimed at reviewing the metabolic changes after LSG among Hong Kong Chinese in a regional hospital.

Materials and methods
47 patients who received LSG in our hospital from June 2008 to October 2012 were retrospectively reviewed. Change in body weight (BW) and glycaemic control up to 5 years were evaluated. Rate of remission of diabetes at 1 year after operation was also reviewed. Statistical method used include Wilcoxon’s signed rank test for paired-related groups and Mann-Whitney U test for paired non-related groups.

Results
The mean age was 43.7 (19–63) years. The mean baseline BW and BMI were 105.7±3.5 and 39.7±4.6 kg/m² respectively. The maximum weight loss was achieved at post-operative 1 year, i.e. 25.1±1.7 kg (23.7±1.49%) (P = 0.00). Significant % weight loss was still maintained at post-operative 5 years i.e. 21.9±1.39% (P = 0.011, n = 9). For diabetic patients, the improvement in diabetic control was already shown before maximum weight loss. The greatest improvement in fasting blood glucose (FBG) was seen at 1 month dropping from 7.8±0.6 to 6.2±0.5 mmol/l (P = 0.00). The HbA1c reduced from baseline of 7.9±0.4 to 6.7±0.3% at 3 months (P < 0.05). At 1 year after operation, patients achieving remission of diabetes showed statistically significant greater % weight loss (24.9±1.3% vs 17.6±3.6%), lower baseline FBG (6.1±0.2 mmol/l vs 10.2±1.0 mmol/l) and shorter duration of diabetes (2.7 years vs 9.6 years) All diabetic patients who were on diet control before operation achieved remission while the rate for those on oral anti-diabetic drugs and insulin were 58.3 and 27.2% respectively. Remission of diabetes was defined as FBG < 7 mmol/l and HbA1c < 6.5% without medication.

Conclusion
LSG showed sustainable weight loss 5 years after operation. Characteristics of patients achieving remission of diabetes were evaluated which helped to predict outcome.

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EP579
Malignant tumours in patients with type 2 diabetes mellitus and obesity
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Backgrounds and aim
Epidemiologic evidence suggests that people with diabetes are at substantially higher risk for many forms of cancer. The aim of the research was to identify cancer incidence distribution in Belarusian patients with type 2 diabetes mellitus.

Methods
The study group included 73 patients: 46 (63%) women (mean age 65 ± 8 years) and 27 (37%) men (70 ± 7 years) with concurrent diabetes and cancer treated at Alexandrov National Cancer Centre of Belarus in 2013. The mean time of type 2 diabetes mellitus course before cancer diagnosis was 7.8 ± 5.8 years. A meaningful association between diabetes and cancer incidence in men and women subgroups were analysed.

Results
Among women breast cancer was the leading malignancy, accounting for 59% (27 patients), corpus uteri cancer mentioned in 15% (seven patients), cervix in 7% (three patients), lung in 4% (two patients), and other localizations occurred in 15% (seven patients). In men subgroup the higher incidence were registered for lung and prostate cancers, accounting 22% (six cases) and 19% (five cases) accordingly, stomach cancer revealed in 15% (four persons), bladder 11% (three persons), kidneys 7% (two persons), and other localisations 26% (seven persons). Multiple primary malignancies were diagnosed in 18% (ten women and three men). The most frequent initial cancer types were women breast (five patients), lung (two patients), and corpus uteri (two patients), the others type made stomach, colon, cervix uteri cancer, and myeloleucosis.

Conclusion
Breast cancer was the predominated neoplasm (59%) in women with diabetes mellitus. The most common cancer in males was lung cancer (22%) and prostate cancer (19%). 18% of the patients with type 2 diabetes mellitus had multiple primary malignancies. Future researches are needed for better understanding of possible biologic links between diabetes and cancer risk.

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EP580
Preoperative endocrinological evaluation of patients apply for bariatric surgery
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Introduction
Since bariatric surgery is considered to be a more effective treatment modality for morbid obesity, a growing number of patients have been referred to endocrinology clinics in order to exclude an underlying cause. Routine preoperative testing to screen Cushing’s syndrome (CS) or hypothyroidism is still debatable. The aim of this study is to evaluate the accuracy of routine testing in preoperative endocrinological evaluation.

Methods/design
Clinical files of 164 patients who applied for bariatric surgery to our outpatient clinic between January 2014 and January 2015 were reviewed. Cortisol levels following low-dose dexamethasone administration, and free thyroxine. TSH were measured to exclude CS and hypothyroidism respectively. Serum cortisol <1.8 µg/dl was the cut-off point for normal suppression. We also have measured HbA1c, insulin, and fasting glucose as part of our pre-surgical protocol. HOMA-IR was used to determine insulin resistance.

Results
One hundred and sixty-four patients (43 men and 121 women) with a mean age of 39.96 ± 10.95 years and a mean BMI of 49.50 ± 3.46 kg/m² were reviewed. Only in one patient pseudo CS was considered. Primary subclinical hypothyroidism was 12% and primary subclinical hyperthyroidism was 1%, while 151 patients were euthyroidic (92%). The prevalence of known diabetes mellitus was 26%. No new patient of diabetes mellitus was diagnosed, while the prevalence of impaired fasting glucose was 38%. Mean HOMA-IR levels were 5.94 ± 3.5 and mean HbA1c levels were 5.6 ± 0.4% when previously known diabetics were excluded.

Conclusion
Routine screening for CS, hypothyroidism seems to be not required and may cause needless expenditures for national health systems in patients who apply for preoperative evaluation for bariatric surgery. For the time being, diagnostic tests for CS and hypothyroidism in morbidly obese patients should be limited to patients who have accompanying more clinical signs and symptoms.

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EP581
Liver enzymes and triglycerides predict biomarkers of insulin sensitivity in obese, non-diabetic adult patients
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Introduction
Obesity is a risk factor for the development of insulin resistance, type 2 diabetes, cardiovascular diseases and non-alcoholic fatty liver disease. The aim of our study was to examine predictive value of liver enzymes in assessing biomarkers of insulin sensitivity in obese, non-diabetic adults.

Methods
1104 obese, non-diabetic adults were included in the study. Patients were divided into two groups: Group A (BMI 30.0–39.9 kg/m², n=499) and Group B (BMI ≥40 kg/m², n=605). After 12 h of fasting, anthropometric evaluation (BMI, waist-to-hip ratio and percentage body fat) was performed and blood levels of glucose, insulin, HbA1c, total cholesterol, HDL, LDL, triglycerides, AST, ALT, γ-GT and CRP were obtained. HOMA-IR was calculated. Multiple linear regression was used for statistical analysis.

Results
We found that ALT, γ-GT and triglycerides are predictors of HOMA-IR score in Group A (R²=0.02, P=0.007; R²=0.04, P=0.001; R²=0.06, P=0.001, respectively), as well as in Group B (R²=0.03, P=0.002; R²=0.07, P=0.001, R²=0.04, P<0.001, respectively). Percentage of body fat predicts HOMA-IR score in Group A (R²=0.02, P=0.021), whereas waist-to-hip ratio predicts HOMA-IR score in Group B (R²=0.05, P<0.001). Moreover, ALT and γ-GT predict HbA1c in Group B (R²=0.03, P<0.001; R²=0.06, P<0.001, respectively).

Conclusion
These results have verified that parameters of insulin sensitivity in obese, non-diabetic patients could be presumed mainly by levels of liver enzymes and triglycerides. Therefore, these data contribute to the essential role of liver function tests in the detection of metabolically abnormal obesity.

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EP582
Neutralophil to lymphocyte ratio as an inflammatory marker in obesity
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Aim
Cardiovascular morbidity and mortality of obesity is associated with classic risk factors, namely dyslipidaemia, hypertension and impaired glucose metabolism.
Aim of this study was to evaluate inflammation as an independent risk factor by using neutrophil to lymphocyte ratio (NLR).

Materials and methods
Patients who admitted to our outpatient clinic between January and December 2014 were assessed retrospectively. Patients diagnosed as diabetes, prediabetes, hypertension, thyroid dysfunction and any acute or chronic inflammatory disorder were excluded. A total of 437 female cases were included in the study. Cases were grouped according to BMI.

Results
Groups were age-matched (P = 0.513). HOMA-IR and triglyceride values were positively, HDL levels were negatively correlated with BMI (P < 0.05). There was no association between LDL values and BMI. There was a statistically significant difference between NLR values of groups 0, 1, 2 and 3. A trend toward higher NLR in group 4 was observed but the difference did not reach statistical significance (P = 0.117). Group 5 however had significantly higher NLR values (P = 0.008).

Conclusion
Increased NLR value is considered as an inflammatory marker and an indicator of cardiovascular risk. Our results established higher NLR values in morbid obesity patients and emphasised the increased cardiovascular risk in morbid obesity.

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**EP583**

A prospective prevalence study of functional adrenal insufficiency and its outcome in acute myocardial infarction in UKMMC
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Introduction
Acute myocardial infarction (AMI) is a stressful condition in which it stimulates the hypothalamus-pituitary-adrenal axis leading to marked increase in the production of cortisol. Adrenal insufficiency (AI) has been shown to be associated with morbidity and mortality in acute coronary syndrome patients. To date, none study has been performed to determine prevalence of AI among patient with AMI.

Objectives
The aim of this study is to determine the prevalence of AI in AMI by using the low dose (LD) and standard dose (SD) synacthen tests and to correlate with morbidity and mortality.

Method
Sixty patients who fulfilled the diagnosis of AMI within 48 h of onset were subjected to LD (1 μg) synacthen test (LDST) followed by a SD (250 μg) synacthen test (SDST) 2 h later. Those who had AI, repeat synacthen test had to perform at day 30 of AMI.

Result
Thirty-five (62.5%) patients had ST elevation AMI and 21 (35.5%) non-ST elevation AMI. Using an increment of <250 nmol/l following LDST and SDST, 39 (69% ) and 2 (3.6%) patients had adrenal insufficiency respectively. Based on LDST, the diagnosis of AI was associated with significant morbidity and mortality. One patient died during the study period and he had very high cortisol levels. Out of 15 patients who underwent repeat synacthen, only two of them had responded to the synacthen test.

Conclusion
Utilising the LDST, adrenal insufficiency was found in 69.6% of AMI patients. Mortality of AMI showed less cortisol increment to LDST but able to reach the peak cortisol level for both tests. Functional AI in AMI takes longer than 30 days to recover.

Disclosure
This study was approved by Research and Ethics committee of the Faculty of Medicine, UKM and the project code was FF-2014-214. Funding for this study was provided by the research Grant of Faculty of Medicine UKM.

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**EP586**

The assessment of environmental and hereditary factors in obesity patients

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The aim of the research was to reveal and assess the interaction between environmental and hereditary factors in obese patients seeking for weight loss.

**Materials and methods**

We analysed the anamnesis of 134 overweight and obese patients, having asked to endocrinologist for losing weight (20 men and 112 women). The mean age of the respondents was 45.78 ± 8.76 years. 15.7% of patients were overweight, and 84.3% were obese. Heritability of obesity was determined according to family history of obesity, anamnesis of diabetes in relatives, childhood appearance of excess body weight. The environmental changes included eating habits, level of physical activity and water regime of participants.

**Results**

The assessment of the hereditary factors of obesity revealed that 76.5% (101 person) had a family history of obesity: 59.7% (80 patients) mentioned excess body weight on the maternal line and 40.3% (54 patients) described obesity for father’s relatives. Diabetes was diagnosed in 14.9% (20 persons) – on the maternal line and in 9.7% (13 persons) on the fatherly line. 41% of respondents (55 patients) remarked childhood obesity in themselves. The analysis of environmental factors showed that 71%, 7% of respondents skipping meals during the day, 15.4% (18 persons) had only one meal, 55.2% (74 persons) had 2-3 meals/day. Everyday moderate activity 30 min or more described only 11% of respondents, physical activity 30 min or less 3 days a week described 46% of patients, 30 min of activity 5-6 times a week 43% patients. The vast majority of patients 97.7% drank <2 l of water per day.

**Conclusions**

The occurrences of obesity relatives was 59.7% on the maternal line, 40.3% on the paternal line. Interaction with environment factors related to low physical activity and inadequate water consumption.

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**EP587**

Significance of cognitive-behavioural therapy in the treatment of obesity

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Introduction

Dietary therapy (DT), programmed physical activity (PPA) and cognitive-behavioural therapy (CBT) are basic measures in the treatment of obesity. CBT applies methods which change eating habits of obese persons, aiming to remove barriers relating DT and PPA. The goal of this study is to try efficiency of applying CBT in the programme for the reduction of body mass of obese persons, vs the application of DT and PPA alone.

**Design**

The study included 60 obese persons, who were divided into two groups (1 and 2), with 30 patients in each group, 20–58 years of age, with the BMI ≥ 30 kg/m² and hyperlipidaemia (LDL-cholesterol ≥ 4.2 mmol/l serum). Patients have not been previously treated for obesity and were unhappy with their weight. Patients from both groups were on hypocaloric diet, individually designed and had programmed physical activity every day. Patient in group 2 underwent group CBT, under the supervision of a psychologist once a week with duration of 120 min, but in group 1 no. Both groups also went to see an endocrinologist six times, on which occasions their body weight, parameters of lipid status serum and level of glucose in serum were measured. Results showed that in group 2, the medium value of BMI reduction after 12 weeks of treatment was 9.5 kg (8.9%), LDL-cholesterol decreased for 34.5%, HDL-cholesterol increased for 2.7%, triglycerides decreased for 15.3%, glycaemia decreased for 14.8%, which is the significantly better metabolic profile, then in group 1.

**Conclusion**

CBT affected the improvement of motivation and readiness of patients to stick to the dietary regimen and physical activity. In designing the program for the reduction of obesity it is necessary to include CBT, which brings significantly better therapy outcomes, then the application of DT and PPA alone.

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**EP588**

Fine motor skill proficiency in obese children

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**Introduction**

Motor skill proficiency has shown to be a key predictor of children’s engagement and enjoyment of regular physical activity. Recent evidence suggests that obese children have increased difficulties in the planning, initiation and control of motor skills compared to their normal weighted peers (D’Hondt et al. 2009, Gentier et al. 2013). These difficulties often manifest themselves as slower or less efficient performance of motor skills. This could impede the performance of everyday activities as well as affect their willingness to engage in physical activity. However the majority of research focuses on gross motor skill performance despite fine motor skills being prerequisites to many activities of daily living.

**Methods**

A sample of a 46 children were equally divided into two groups (obese (OB) vs normal weight (NW)) based on their BMI calculated using the IOTF cut points for children (Cole et al. 2000). Each group were equally matched for gender (11 male and 12 Female) and age (M = 9.101 s.d. = 1.832 and M = 9.103 s.d. = 1.746). The children were tested using the Fine Motor Skills Composite of the Bruininks Oseretsky Test of Motor Proficiency (BOT-2). The children’s raw scores were converted according to the manual into standardised scores based on normative data.

**Results**

The OB group (M = 46.13, s.d. = 9.16) was found to score significantly lower (P<0.05) than their NW (M = 52.04, s.d. = 5.36) peers using the standard scores of the Fine Motor Skill Composite. This score represents whether a child possesses the expected level of fine motor skill for their age/gender.

**Conclusion**

The assumption that mass alone is responsible for these differences between BMI groups is not sufficient as additional body mass would only have a limited effect on fine motor skill. The above findings suggest the existence of a deficit in how OB children integrate and process sensory information compared to their normal weighted peers.

**Disclosure**

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**EP589**

High mean platelet volume in morbid obesity

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Introduction and aim

The incidence of atherosclerotic vascular disease is high in obesity. Our aim is to determine the mean platelet volume (MPV) as a new indicator of atherosclerosis in morbid obesity.

**Materials and methods**

Thirty-three patients with morbid obesity who applied to endocrinology department (mean age 41.5±1.13 years, body weight 118.2±16.9 kg and BMI: 45.9±7.2 kg/m²) and 39 age-matched (mean age 35.3±13.1 years; body weight 60.4±11.3 kg; BMI: 21.6±2.6 kg/m²) healthy individuals were included in the study. Patients have haematological and other endocrinological diseases.
 EP590  
**Genetic variation in GLP1 receptor is associated with interindividual differences in weight lowering potential of liraglutide in obese women with PCOS**  
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**Objective**  
The weight lowering potential of glucagon-like peptide (GLP) 1 receptor agonists (RAs) is interindividually different and clinically unpredictable. The potential role of genetic variability of GLP1R on body weight response to GLP1 RA has not yet been evaluated. The aim of the study was to assess the effect of common non-synonymous GLP1R single nucleotide polymorphisms (SNPs) rs6923761 and rs10305420 on weight loss in response to long acting GLP1 RA liraglutide in obese women with PCOS.

**Methods**  
59 obese women with PCOS (aged 30.7±6.9, BMI 38.4±5.3 kg/m²) were assigned to liraglutide 1.2 mg QD sc. for 12 weeks. They were genotyped for GLP1R rs6923761 and rs10305420. Changes of body mass, BMI, waist circumference and visceral adipose tissue (VAT) area were measured before and at the end of the study.

**Results**  
After treatment intervention women lost on average 3.96±3.24 kg (P<0.001), BMI was reduced for 1.44±1.22 kg/m² (P<0.001), waist circumference for 3.31±4.13 cm (P<0.001) and VAT for 7.05±8.55 cm² (P=0.002). Twenty (34%) out of 59 subjects were good responders and lost 5% or more of their initial body weight. Carriers of at least one polymorphic rs10305420 allele had worse treatment response compared to carriers of two WT alleles (OR=0.27, 95% CI=0.09-0.85, P=0.025). Carriers of at least one polymorphic rs6923761 allele tended to have better treatment response compared to carriers of two WT alleles, but the difference was not statistically significant (OR=3.06, 95% CI=0.96-9.74, P=0.058).

**Conclusion**  
Polymorphism of GLP1R rs10305420 accounts for interindividual differences in response to liraglutide regarding weight loss in obese women with PCOS. Future studies will determine whether such genetic variation may be clinically useful in prediction of the weight lowering potential of GLP1 RAs in obese individuals.

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 EP592  
**Relationship between thyroid hormone status and concomitant medication in hyperlipidaemic patients with statin induced adverse effects**  
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**Aims**  
The aim of our study is to assess the efficacy of lifestyle modification in preventing diabetes mellitus type 2 (DM 2) and hypercholesterolemia.

**Materials and methods**  
The study included 100 patients (69 m 258 f) aged 25–65 years with impaired glucose tolerance/impaired fasting glucose (IGT/IFG) and newly diagnosed DM 2. Patients were divided into two groups matched by sex, age, weight, BMI, waist-to-hip ratio (WHR). Research group included 54 patients who received and carried out recommendations of a balanced diet and physical activity. Control group included 46 patients who did not lifestyle modification. The study was 48 weeks. We measured fasting plasma glucose (FPG), 2-h plasma glucose concentrations (2-h PG) following a 75-g oral glucose tolerance test and related to fasting leptin (FL).

**Results**  
Patients of the research group demonstrated reduction of BMI (−2.3±3.1 kg/m²) and WHR (−0.02±0.205) (P<0.01 for all). They had positive dynamics of FPG and 2-h PG concentrations (P<0.001). Persons of the control group had increase BMI and WHR as also FPG and 2-h PG concentrations elevation (P<0.05). The main novel finding was that median serum leptin in research group decreased on −23.9% (P<0.01) and increased in control group on +27.6% (P<0.01). Among subjects with IGT from the research group, glucose levels normalised in 49.3% (P<0.001) and serum leptin levels decreased on 26.9% (P<0.01). In control group glucose levels normalised in 4.5% (P<0.01) persons with IGT. By the end of the study 12% of non-diabetic subjects with obese have developed DM 2 and 48% IGT. Among patients of the research group was a reduction of DM 2 by 11.9% and an increase in the control group by 35.1%

**Conclusion**  
Thereby, lifestyle modifications lead to reduction not only fasting plasma glucose, 2-h plasma glucose concentrations but and fasting leptin concentrations in individuals with impaired glucose tolerance.

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EP593
Is there a relationship between parathyroid hormone and obesity-linked disorders
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Introduction
Accumulating evidence indicate that high PTH resulting from primary or secondary hyperparathyroidism, is associated with hypertension, insulin resistance, dyslipidaemia, obesity, and cardiovascular mortality. Here, we aimed to show whether high PTH levels in obese population contribute the metabolic complications of obesity.

Methods/design
The medical records of all subjects attending the obesity outpatient clinic of Kartal Dr Lutfi Kirdar Training and Research Hospital in Istanbul between April 2014 and January 2015 were retrospectively evaluated. Subjects who had chronic illness, endocrine disease (diabetes mellitus, thyroid dysfunction, Cushings disease) and subjects with any medication were excluded. A total of 400 obese patients included in the study. Anthropometric, bioelectrical bioimpedence measures, blood examinations and 75-g glucose tolerance tests results were evaluated. Data are presented as means ± s.d.s for continuous or median (25 and 75% interquartiles) for non-normally distributed variables.

Results
Of the 400 obese subjects 335 were female. Mean age was 39 ± 10. Median BMI was 36 (34–41). Subjects were divided to quartiles according to blood PTH levels. Groups included Quartile 1 (n = 100, median PTH; 42 (36–45)), Quartile 2 (n = 100, median PTH; 55 (51–59)), Quartile 3 (n = 100, median PTH; 73 (68–78)), Quartile 4 (n = 100, median PTH, 99 (89–125)). Quartiles were evaluated with generalized linear model adjusted for age, sex and season of recruitment. Log was performed for non-normally distributed variables. Systolic and dystolic blood pressure, HOMA-IR, insulin sensitivity index (ISI), triglyceride (TG), HDL-cholesterol were not different among quartiles. Although, BMI was not associated with trunk MBF and PTF, but was not associated with obesity linked metabolic parameters.

Conclusion
Serum PTH adjusted for age, sex and season of recruitment, is positively associated with trunk MBF and PTF, but was not associated with obesity linked metabolic parameters.

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EP594
Cardiovascular disease in patients with primary hyperparathyroidism
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Introduction
Patients with primary hyperparathyroidism (PHPT) have an increased cardiovascular risk. However, the data on the relationship severity of PHPT clinical forms and prevalence of cardiovascular disorders are controversial.

Objective
The aim of the study was to evaluate cardiovascular disease in patients with manifest forms of PHPT compared with mild forms.

Materials and methods
We studied 136 patients with PHPT (assesses arrhythmias, hypertension, coronary disease), a general medical examination were made. The indicators calcium and phosphorus metabolism (PTH, vitamin D, Ca general, Ca++, phosphates) were investigated.

Results
The mild PHPT were diagnosed in 54 patients with a mean age of patients was 51.5 ± 11.6 years, manifest forms PHPT were diagnosed in 82 patients, the average age of the patients was 52 ± 10.4 years. Cardiovascular disease were found in 19 (35.1%) patients with mild forms of PHPT and 38 (45.2%) with the manifested PHPT. A strong statistically significant correlation between the severity of clinical manifestations PHPT and incidence of cardiovascular disease in patients with PHPT (R = 0.81, P < 0.05).

Conclusion
These results suggest the high incidence of cardiovascular disease in patients with manifested PHPT and the low diagnostic rate of mild forms of PHPT.

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EP595
N-terminal pro-brain natriuretic peptide – an early independent predictor of anthracycline-induced cardiomyopathy
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Introduction
Early prediction of anticancer therapy cardiotoxicity is essential for applying proper preventive and supporting therapeutic strategies.

Objective
To evaluate plasma N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) related to cardiac dysfunction assessed by transthoracic 2D echocardiography (2D-TTE) in patients with cancer and early onset asymptomatic anthracycline-induced cardiomyopathy (AIC).

Methods
Prospective study of 68 patients with cancer treated with anthracyclines, followed up for 6 months. Diagnosis of AIC was set at 6 months by decreasing of left ventricular ejection fraction (LVEF) below 50% or with more than ten units or 20% from baseline. NT-proBNP and 2D-TTE were assessed at enrolment, and thereafter at 3 and 6 months.

Results
Fifteen (22.1%) patients developed AIC at 6 months of anthracycline treatment (group 1), and 53 (77.9%) patients did not evolve with AIC (group 2). At 3 months, in patients from group 1 NT-proBNP was significantly higher compared to group 2 (121.0 (119.8; 140.8) pg/ml vs 97.7 (75.5; 111.7) pg/ml, P = 0.0001, values expressed as median (25th; 75th percentiles)). Left ventricular (LV) diastolic dysfunction was significantly more frequent in group 1 (93.3%) vs group 2 (37.7%), P = 0.0002. NT-proBNP at 3 months proved accurate in predicting asymptomatic AIC at 6 months (area under the receiver operating characteristic curve (AUC) = 0.845, 95% CI: 0.735–0.954, P = 0.0001). New-installed diastolic dysfunction at 3 months had a sensitivity of 60%, a specificity of 77% in predicting AIC at 6 months. NT-proBNP assessed at 3 months above a cut-off = 118.5 pg/ml was an independent predictor of AIC at 6 months.

Conclusions
Plasma NT-proBNP at 3 months of anthracycline therapy proved to be an early independent predictor of asymptomatic anthracycline-induced cardiomyopathy.

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EP596
Increased expression of ATP-binding cassette transporter A1 by cilostazol may be a possible mechanism for its protective effect against hepatic steatosis
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Objective
Cilostazol, a selective inhibitor of phosphodiesterase 3, which has been widely used in patients with atherosclerotic diseases, is known to have additional beneficial effects on dyslipidemia. ATP-binding cassette transporter A1 (ABCA1) plays a critical role in the regulation of intracellular cholesterol levels in hepatocytes. We aimed to investigate the effect of Cilostazol on hepatic steatosis and its underlying mechanism related to ABCA1.

Methods
Male C57BL/6 mice were randomly divided into three groups: i) fed normal chow diet with vehicle. ii) fed high-fat diet (HFD) with vehicle. iii) fed HFD with
Cilostazol. Cilostazol (30 mg/kg) was orally administered once daily for 9 weeks. Oral glucose tolerance test was done and liver tissues were examined. Hep2G cells were also used as an in vitro model by incubating with saturated fatty acid (palmitate) in the presence or absence of Cilostazol.

Results
In HFD-fed mice, Cilostazol treatment significantly decreased hepatic fat and liver weight. Cilostazol-treated mice also showed improved glucose tolerance and decreased levels of serum LDL, VLDL and total cholesterol. The expression of ABCA1 was significantly increased in the liver of cilostazol-treated mice by 2.4-folds (P < 0.05) compared to HFD-fed control mice. In paclitaxel-treated Hep2G cells, lipid accumulation was significantly decreased after treatment with Cilostazol. Palmitate reduced the expression of ABCA1, which was restored with Cilostazol treatment by 1.3-folds (P < 0.05). The HDL-cholesterol levels in the cell cultured media were also increased, while intracellular LDL and VLDL-cholesterol levels were decreased in Hep2G cells treated with palmitate and cilostazol compared to those with palmitate only.

Conclusion
Our results showed that cilostazol ameliorated hepatic steatosis by increasing ABCA1 expression in the hepatocytes. This implicates that cilostazol may have a beneficial role in the treatment of non-alcoholic fatty liver disease.

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EP597

Exploratory study a Brazilian population with multiple chronic conditions from the perspective of smoking
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Recent evidence shows that are modifiable risk factors and preventable, the most responsible for the high morbidity and mortality to multiple chronic conditions (MCC), and smoking is one of the most important representative. However, we still lack studies of populations with MCC and its association with smoking status.

Objectives
To identify clinical and psychosocial characteristics according to the status of smoking among users with MCC, at high cardiovascular risk.

Methods
Cross-sectional study with evaluation of socio-demographic, clinical and laboratory data, in HIPERDIA Center Juiz de Fora, Minas Gerais (CHM-JF), Brazil, assisting users with MCC (hypertension, diabetes mellitus and chronic kidney disease). To check the status of smoking was considered smokers (S), former smokers (FS) and nonsmokers (NS). Control blood pressure (systolic blood pressure < 130 mmHg); metabolic (normal fasting blood glucose <100 mg/dl and/or regular glycated hemoglobin <7%, for users <60 and <8% for those with ≥60 years); Normal LDL-cholesterol (<100 mg/dl); chronic kidney disease absent, the glomerular filtration rate (GFR) ≥ 60 ml/min per SC. Depression (PHQ-2 ≥ 3 points) and alcohol abuse (AUDIT-C > 5 points). Declared atherosclerotic disease, DAD (vascular damage documented, regardless of the affected territory).

Results
1558 users reviews, of which 12% were S; 41% and 47%, FS and NS. Compared to FS and NS, S were younger, less obese and more often female, higher prevalence of low education, physical inactivity, depression, alcohol abuse and lack lipid. Additionally, FS had better lipid control in relation to S and NS. Chronic obstructive pulmonary disease (COPD) and DAD were more prevalent among S and FS, even after adjusting for confounding variables.

Conclusion
The current smoking was more common in the younger population, sedentary, alcohol abuse, depressive symptoms, users declared atherosclerotic disease, COPD and a history of cancer. These data gave to S, a worse clinical profile compared to the NS. For despite the termination, the FS remained with similar comorbidities that active smokers.

Disclosure
The project was approved by the Research Ethics Committee of the Federal University of Juiz de Fora, Opinion 283/2011 in 24/04/2012, funded by the National Institutes of Health Fogarty.

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EP598

TNFα induces lipolysis by downregulating CIDEC via MEK/ERK-dependent PPARγ phosphorylation and nuclear exportation
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CIDEC is a lipid droplet-targeting protein that promotes triglyceride accumulation and inhibits lipolysis. CIDE/ is regulated by peroxisome proliferator-activated receptor γ (PPARγ). Previous studies demonstrate that CIDE/C down-regulation is involved in TNFα-induced lipolysis. Here, we focus on the signalling pathway to clarify the mechanism of TNFα-mediated CIDEC down-regulation. CIDEC is significantly decreased in subcutaneous adipose tissue in obese subjects. Also, CIDEC mRNA expression inversely correlates with serum TNFα levels in our cohort of 68 patients. Using SW872 human adipocytes-differentiation model, we verify that TNFs causes lipolysis and CIDEC down-regulation in a dose and time-dependent manner. 10 mg/ml TNFα almost abolishes CIDEC protein expression at 12h exposure, while the MEK/ERK inhibitor U0126, but not the JNK inhibitor SP600125 or the p38 inhibitor SB203580, blocks this response. In addition, RNAi Knockdown of ERK1/2 inhibits TNFα-induced CIDEC down-regulation and phosphorylation of PPARγ. Furthermore, depletion of MEK1/2 which are the upstream activators of ERK1/2 reverse CIDEC down-regulation to a larger extent. Immunostaining of PPARγ and subcellular fractionation confirm that MEK1/2 rather than ERK1/2 mediate PPARγ nuclear exportation. Taken together, TNFα down-regulates CIDEC protein levels due to phosphorylation and nuclear export of PPARγ by MEK/ERK cascade and this adds new aspects of TNFα-induced lipolysis.

Disclosure
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EP599

Magnitude of overweight and obesity amongst school children in Delhi, India
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Obesity has emerged as epidemic in India. In the present study was conducted to assess the magnitude of overweight and obesity amongst children in the age group of 5–18 years belonging to low, middle and high income group in National Capital Territory NCT of Delhi. A total of 16 595 children (LIG 5087, MIG 5134 and HIG 6538) were covered in the present study. Overweight and obesity were assessed using BMI and triceps skin fold thickness (TSFT) utilizing age and sex specific cut off points. Considering the BMI cut off points, the prevalence of obesity and overweight in Low Income Group (LIG) school children was 0.1 and 2.7%, respectively, amongst Middle Income Group (MIG) school children it was 0.6 and 6.5% and in High Income Group (HIG) school children was 6.8 and 15.3% respectively (P < 0.001). With regard to the TSFT criteria, the prevalence of obesity and overweight in LIG school children was 1.2 and 2.4%, amongst MIG school children it was 2.5 and 4.9% and in children belonging to HIG schools was 9.3 and 13.1% respectively (P < 0.001). The present study documented that the prevalence of overweight and obesity was higher in the HIG children as compared to the MIG and the LIG for all age groups, highlighting the possible role of change in the dietary pattern and physical activities with increase in income levels.

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Altered sensory motor integration of obese adults

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Introduction
It appears recently that the lack of physical activity might not be a factor for obesity but rather a consequence of perceptual-motor difficulties (D’Hondt et al. 2011). Perception and action are two intertwined processes: perception is a means to action and action is a means to perception. Not being able to perceive correctly visual or auditory information would alter someone’s movement kinematics of any given task. The key question is how do these different senses interact in situations that rely on the tight coupling between perception and action? To which extent obesity modifies the sensory motor integration and the movement output?

Methods
88 participants (44 Obese and 44 matched-control) sat on a chair equipped with a wrist pendulum that moves in the sagittal plane. The pendulum had a potentiometer built-in that records the angular wrist movement. For one of the experimental conditions, an oscillating visual stimulus was displayed on the screen. Another experimental condition consisted of an auditory signal oscillating between the right and left ears of the participants. The task was to synchronise the pendulum with either or both sensory modalities.

Results
The key findings from the repeated-measures ANOVAs revealed a strong reduction of the movement accuracy of the obese participants. For all sensory modalities, patients struggled to synchronise their action with the stimuli (P<0.05). To make an analogy with a dance performance, one can imagine someone dancing off the beat of the music. The movement variability of the obese participants was also higher than the control group (P<0.05).

Conclusion
This perceptual problem reduces the motor control of obese patients revealing even more encompassed difficulties. The identification of the origin of the perceptual problem will allow us to address the problem to its source and eventually to break the vicious circle of a deficient perception and action coupling.

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The effectiveness of an integrated approach in the treatment of obesity

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Introduction
To assess the effectiveness of treatment of obesity using complex integrated approach. In the treatment of obesity were used: instructions of patient in healthy eating habits, diet, taking medication that reduces fat absorption – lipid-adsorbent tablets, polyglucosamine (L112). Survey of patients was conducted. The received data were analysed.

Description of methods
61 obese patients (18 males and 43 females) were followed up for 12 weeks. Mean age: 48.2±9.2 years; BMI: 34.9±5.21 kg/m², BML waist circumference (WC) measurements, visceral fat content (%) before and after treatment were measured. Levels of total cholesterol (TC), triglycerides (TG), LDL cholesterol (LDLC), and HDL cholesterol (HDLC) were also measured.

Results
Followed up patients reached weight loss by 3.7%, in BMI of 1.31 kg/m², WC 5.21 kg/m². BMI, waist circumference (WC) significantly decreased during 12 weeks. Combination of drug treatment and methods could be important factor for weight loss. In this case treatment was effective.

Conclusion
An integrated approach in treatment of obesity is effective and consists of education of patients, presence of motivational reasons to lose weight, level of education, adherence to the principles of healthy eating and receiving supplementary medication to reduce fat absorption.

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Low plasma SHBG levels in overweight individuals are a biomarker for the metabolic syndrome and are predictive of type 2 diabetes and risk of cardiovascular disease. There are no in vivo models to study SHBG expression and regulation during obesity development. The main reason for this is that the obesity-prone rodent models cannot be used to study this issue since rodents unlike humans do not express the SHBG gene in their livers. We have developed by crossing the human SHBG transgenic mice with the C57BL/ksJ-db/db mice, a unique mouse model that expresses the human SHBG and it develops obesity. We have also used a set of human liver biopsies. The results obtained with the SHBG-C57BL/ksJ-db/db mouse model have allowed us to determine that the SHBG overexpression in the C57BL/ksJ-db/db reduced the body weight gain but did not change the metabolic profile of these mice. Moreover, we elucidated the molecular mechanisms and transcription factors causing the SHBG downregulation during obesity development, which involved changes in liver hepatocyte nuclear factor 4 alpha (HNF4α) and peroxisome proliferator-activated receptor gamma (PPARγ) mRNA and protein levels. Furthermore, these results were confirmed using human liver biopsies. Finally, obese mice had reduced plasma SHBG and total and free testosterone levels when compared to lean mice. We have created the first mouse model that resembles what occurs in human obese subjects in terms of SHBG expression and regulation as well as the reduction of total and free testosterone levels. Future research using this unique mouse model will determine the role of SHBG in the development and progression of obesity, type 2 diabetes or fatty liver disease.

Disclosure
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Adiponectin deletion impairs insulin signalling in insulin-sensitive but not insulin-resistant 3T3-L1 adipocytes

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Aims
Previous reports have demonstrated that the adipocyte-derived peptide adiponectin is closely associated with insulin resistance due to its insulin-sensitizing and anti-inflammatory properties in peripheral tissues; however the autocrine effects of adiponectin remain elusive. This study investigated regulatory effects of adiponectin on glucose transport and insulin signalling in insulin-sensitive or insulin-resistant 3T3-L1 adipocytes.

Methods
3T3-L1 fibroblasts were transduced with non-target or adiponectin (ADN) siRNA and differentiated. Chronic treatment with insulin (24 h, 100 nM) was employed to induce insulin resistance in differentiated adipocytes. Insulin-stimulated glucose transport was measured and protein and mRNA levels were assessed by western blot and RT-PCR.

Results
Prolonged incubation with insulin significantly reduced insulin-stimulated glucose uptake, suggesting the development of insulin resistance and adiponectin mRNA expression. In this insulin-resistant condition, adiponectin deletion did not alter insulin-stimulated glucose uptake. In insulin-sensitive adipocytes, adiponectin deletion reduced insulin-stimulated glucose uptake, expression of IRS-1 and GLUT4, and GLUT4 translocation to the membrane. Adiponectin knockdown did not affect the activation of AKT and p38MAPK (phosphorylation form/total form), but significantly decreased the activation of AMPK in insulin-responsive adipocytes.

Conclusion
Adiponectin deficiency suppresses insulin-induced glucose uptake, insulin signalling, and the AMPK pathway only in insulin-responsive 3T3-L1 adipocytes.

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WHO is the Belarusian citizen seeking for losing weight?!

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Backgrounds and aim
Millions of people all over the world are in a search for the perfect weight loss plan. The aim of our research was to make a typical portrait of a Belarusian citizen who is trying to lose weight.

Methods
Participants were individuals (n = 70) who were screened for a behavioral weight-loss treatment program. The majority of patients were women (88.4%). The mean age was 46.56 ± 9.43 years. Among the participants three of 70 persons had normal BMI but felt themselves fat, 13 patients were overweight and 53 were obese (23 persons had BMI 30–34.9 kg/m²; 14 persons – BMI 35.0–39.9 kg/m²; and 17 persons BMI > 40 kg/m²). We analyzed the anamnesis of obesity, eating habits, physical activity, and comorbidity of the participants.

Results
We revealed that 18 of 67 participants (26.8%) had the excess weight from childhood, 17% of women become overweight after delivery. 41 of 67 persons (61.2%) had obese relatives on the maternal line, 28 of 67 persons (41.8%) on the paternal line. Among the participants 17 of 67 participants (25.3%) had hypertension and cardiovascular diseases, four of 67 (6%) registered hyperglycemia, 22.3% osteoarthritis. The majority of patients 52.2% made attempts to lose weight earlier; 47.7% of the participants follow unproven dieting advices; 19.4% used supplements and diet pills. The analyses of the eating habits revealed that 37.3% follow the starvation diet; 31.3% of participants were breakfast skippers. Physical activity < 30 min five times per week was registered in 65.6% cases. The episodes of night eating described 8.9% participants. 13.4% of respondents felt teasing and social rejection.

Conclusion
Thus the typical obese Belarusian patient looking for losing weight is a women of 46.5 years old, who often had a severe anamnesis of obesity, series of comorbidities, and disordered eating patterns.

Disclosure

EP605
Long-term glucocorticoid concentrations as a risk factor for childhood obesity and adverse body fat distribution
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Background
Childhood obesity is an increasing health problem, affecting over 40 million children aged 0–5 years worldwide. It is associated with premature onset of diabetes and cardiovascular disease in adulthood. Pathologically elevated cortisol is known to induce obesity and cardio-metabolic complications, suggesting cortisol is implicated in the onset of obesity. Indeed, recent pilot-studies showed an increase in hair cortisol concentrations in obese adults and adolescents. Additionally, polymorphisms in the glucocorticoid receptor (GR) gene increasing glucocorticoid (GC) sensitivity have been associated with metabolically adverse body composition.

Aim
To explore the role of GCs in the onset of obesity, we studied the associations of long-term GC exposure and genetically determined GC sensitivity with obesity and body fat distribution in children.

Methods
Average cortisol and cortisone concentrations over a 3-month period were measured by LC–MS/MS in scalp hair of 3019 6-year-old children participating in the Generation R study, a population-based cohort-study. Four polymorphisms (GR-9Beta, ERZ2-23EK, N363S, Bcl1) in the GR gene affecting GC sensitivity were genotyped. Anthropometrics were measured and DEXA scans were performed. World Obesity Federation criteria for weight-cutoffs were used.

Results
A total of 4.3% of the children were obese and 13.4% overweight. Long-term cortisol concentrations were associated with obesity (OR 10.3, P < 0.001) and overweight (OR 1.5, P < 0.05). Cortisone showed the same trend for obesity (OR 2.1, P < 0.05), and overweight (OR 1.4, P = 0.08). Cortisol and cortisone showed a positive linear association with BMI (P < 0.001 and P < 0.01), fat mass index (kg/height²) (P < 0.01 and P < 0.001) and android/gynecoid fat mass ratio (P < 0.04 and P < 0.001). Fat mass index was increased in homozygous Bcl1 – carriers (P = 0.03). We found no effects of other polymorphisms.

Conclusion
Long-term GC levels are strongly associated with an increased risk of childhood obesity, and show linear associations with adverse fat distribution. The contribution of GR gene polymorphisms to body composition at the age of 6 years seems limited.

Disclosure
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EP606
From genome to gene: genes and genetic variations to be associated with metabolic syndrome
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Introduction
The prevalence of non-communicable disorders such as metabolic syndrome (MetS) is high in developing countries. MetS is a disorder of energy utilisation and storage, diagnosed by a co-occurrence of three out of five of the following medical conditions: abdominal (central) obesity, elevated blood pressure, elevated fasting plasma glucose, high serum triglycerides, and low HDL cholesterol levels. The present review aims to discover the genetic variant reported in association with MetS.

Method and materials
The database for genotypes and phenotypes (dbGaP) and the database for genetic associations and human genome (HuGE navigator) were utilised in order to search for genes and their corresponding polymorphisms related to MetS. Additionally, an electronic literature search for other Iranian studies and the genetic aspect of TLGS was completed using PubMed.

Results
For phenotype selection in PharGen, 30 traits were chosen and after the analysis, 21 of them were in common results with MetS. After finding the common variation between traits and MetS, omitting the repeated SNPs, 173 variations were remained. Finally, results distinguished six of the most important genetic regions found to have strong association with MetS.

Conclusion
Identifying major genes that are responsible for the MetS may improve the medical care for treating individuals with MetS, and eventually may lead to personalised medicine in which treatment is tailored genetically to the patient’s needs. The present candidate regions is a respectable start to replicate genetic studies in large affected Iranian individual which we hope leads us to improve our medical care in this field.

Disclosure

EP607
Audit of metabolic profiles in women with Turner syndrome
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Introduction
Adults with Turner syndrome (TS) are at increased risk of cardiovascular morbidity and mortality. The aim of this study was to evaluate the compliance
with clinical guidelines (Bonyd 2007) in measuring metabolic profiles in adults with TS.

Methods
Case notes of patients attending a dedicated TS clinic were studied. Variables assessed included anthropometric measurements, blood pressure (BP), fasting plasma glucose (FPG), HbA1c, fasting lipid profile, and thyroid function.

Results
Of 40 women with TS (mean age 35.9 years (18–56 years)), karyotyping was available on 70%: 17.5% had monosomy (45,X); 52.5% had other X chromosome abnormalities (mosaic 45,X/46,XX, ring X chromosome, isochromosome Xq, deletions Xp, and other structural abnormality of Y chromosome). Anthropometric and BP measurements were performed in all patients. FPG, HbA1c, fasting lipid profile, and thyroid function were measured in 90, 82, 92.5, and 100% of women, respectively. 27.5% were overweight and 35% were obese. 10% had impaired glucose tolerance and 7.5% had type 2 diabetes mellitus. 67.5% had LDL-cholesterol between 2.5 and 4 mmol/l and 7.5% had LDL-cholesterol more than 4 mmol/l. 15% had triglycerides level between 1.7 and 2.3 mmol/l and 5% had triglycerides more than 2.3 mmol/l. 27.5% were on antihypertensive medications. 17.5% were on cholesterol-lowering medications. 40% had primary hypothyroidism on L-thyroxine replacement. Systolic BP was significantly higher in monosomy group than those with other X chromosome abnormalities (128 ± 7 mmHg vs 117 ± 12 mmHg; P = 0.034). There were no significant differences in age, BMI, diastolic BP, HbA1c, lipid profiles, use of cholesterol-lowering medications or HRT between women with monosomy and those with other X chromosome abnormalities.

Conclusion
Service evaluation reveals good performance in measuring metabolic parameters in women with TS. Overweight/obesity, hypertension, and dyslipidaemia are common in our group of patients. Ongoing efforts are aimed at improving these Cardiovascular risk factors.

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EP608
Metabolic syndrome and cardiovascular risk in frail elderly people
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Introduction
Objective of this study was to examine the importance of metabolic syndrome (MetS) as a predictor of cardiovascular mortality in frail elderly people.

Methods
Participants of the study were 253 community dwelling elderly aged 65–99 years. The baseline mean age of participants was 82 years (78.3% women) (53.8% had triglycerides more than 2.3 mmol/l. 15% had triglycerides level between 1.7 and 2.3 mmol/l and 5% had triglycerides more than 2.3 mmol/l. 27.5% were on antihypertensive medications. 17.5% were on cholesterol-lowering medications. 40% had primary hypothyroidism on L-thyroxine replacement. Systolic BP was significantly higher in monosomy group than those with other X chromosome abnormalities (128 ± 7 mmHg vs 117 ± 12 mmHg; P = 0.034). There were no significant differences in age, BMI, diastolic BP, HbA1c, lipid profiles, use of cholesterol-lowering medications or HRT between women with monosomy and those with other X chromosome abnormalities.

Conclusion
Service evaluation reveals good performance in measuring metabolic parameters in women with TS. Overweight/obesity, hypertension, and dyslipidaemia are common in our group of patients. Ongoing efforts are aimed at improving these Cardiovascular risk factors.

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EP609
Investigation of the transient receptor potential channel gene expressions in metabolic syndrome
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Introduction
Metabolic syndrome (MetS) is correlated with increased cardiovascular risk and characterized by several factors, including visceral obesity, hypertension, dyslipidemia, and insulin resistance. Several members of a large family of nonselective cation channels, e.g., transient receptor potential (TRP) channels, have been associated with the development of cardiovascular diseases. Thus, changes of TRP channel expression may account for the observed increased cardiovascular risk in MetS patients. The aim of this study was to investigate the possible contribution of TRP channel gene expressions in MetS.

Methods
A total of 54 patients with obesity-related MetS, and 41 healthy control subjects with similar age and sex were included to this study. mRNA from blood samples was extracted, and real-time PCR on the BioMark HD dynamic array system (Fluidigm, South San Francisco, CA, USA) was performed for the TRP channel gene expressions. For calculation of the significance of differences in gene expressions, the Mann-Whitney U test was used.

Results
We observed marked decreases in TRPC1, TRPC3, TRPM2, TRPM5, TRPV4, TRPV5, TRPV6, MCOLN2 (TRPM2L), and MCOLN3 (TRPM3) gene expressions in MetS (P < 0.05). However, there was an augmentation in TRPC6 gene expression (P < 0.05). No significant changes in expressions were found with TRPA1, TRPC4, TRPC5, TRPC7, TRPM1, TRPM3, TRPM4, TRPM6, TRPM7, TRPM8, TRPV1, TRPV2, TRPV3, MCOLN1 (TRPM1L), and PKD2 (TRPP2) genes in MetS patients (P > 0.05).

Conclusion
This study revealed that there is a statistically significant relationship between TRP channel gene expressions and MetS. Our data showed that TRP channel gene expressions may contribute to the pathology of MetS.

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EP610
Linking temperature to metabolism: the role of brown adipose tissue in humans
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The increasing prevalence of obesity is paralleled by related metabolic disorders such as insulin resistance and type 2 diabetes mellitus (T2DM). Extensive efforts across disciplines are made to reveal underlying mechanisms and develop effective therapies against obesity and its comorbidities. Since PET–CT studies provided evidence for functional brown adipose tissue (BAT) in adult humans, this specialized thermogenic compartment of adipocytes is in the focus of current research. Activated by moderate cold BAT utilises significant amounts of carbohydrates and fatty acids as substrates for heat production, thereby contributing to whole-body energy homeostasis. Beneficial metabolic effects of BAT activation lipid metabolism have been shown in mice and men. Here we assessed glucose homeostasis by Botnia clamping during cold-induced BAT activation in 15 healthy normal-weight men. Botnia clamp experiments combine an intravenous glucose tolerance test with a subsequent hyperinsulinaemic–euglycaemic clamp thereby allowing measurement of pancreatic β-cell capacity and peripheral insulin sensitivity within one session. BAT activation induced a highly significant 20% increase in glucose uptake due to improved insulin sensitivity while β-cell capacity remained unchanged as compared to thermoneutral conditions. Interestingly, resting energy expenditure and pituitary–thyroid axis activity as possible pathways linking BAT activation and glucose homeostasis were not affected during BAT activation. Although, underlying molecular mechanisms remain to be established in follow-up studies, these findings clearly highlight the metabolic significance of BAT activation in men and therefore might be a promising target for novel treatment approaches in obesity and T2DM.
EP611
C-reactive protein assay in obese paediatric patients: comparison of two laboratory methods
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Introduction
Obesity as a pro-inflammatory state is associated to increased levels of C-reactive protein (CRP). CRP is considered as a cardiovascular (CV) risk independent marker and is being researched as a predictive atherosclerosis biomarker in obese children. The American Heart Association (AHA) recommends three classes approach when aiming at CV risk stratification (low <1.0 mg/l; moderate 1.0–3.0 mg/l; and high >3.0 mg/l). These classes were extrapolated to the paediatric aged patients.

Objective
Compare the performance of two different CPR assays, using blood samples from an obese paediatric population.

Methods
79 patients were enrolled (convenience sample) (ages 12–17). Serum CPR levels were simultaneously assayed using two distinct analytical methods: Classic wide range CPR assay (wCRP Siemens Lexis enhanced immunoturbidimetry; ADVIA 2400; CMD =0.03 mg/l normalization; CRM 470 IFCC), and high sensitivity PCR (CardioPhase hsCRP Siemens BNproSpec Siemens CMD =0.175 mg/l). SPSS 20V Software was used for statistical analysis.

Results
The correlation coefficient ($R$ =0.9971) ($P$<0.001) (Pearson’s test) showed a very strong positive correlation between the two assays ($y$=1.26–0.34). The Bland–Altman dispersion plot, pointed that the inter assay (absolute (AD) and percentual (PD)) differences were in 95% CI (except one outlier (>10 mg/l) (AD) and the six lowest pairs (PD)). PCR values of both assays were stratified according to AHA CV risk classes (72 pairs (91.14%) were grouped in the same class, including the aforementioned six lowest pairs). The Fleiss’ test ($κ$ =0.858) ($P$<0.001) showed a very strong AHA class agreement of both assays.

Conclusion
A strong correlation and agreement has been shown between the two assays.

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EP612
Does IGF1 influence the prognosis 10 months after myocardial infarction?
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Introduction
We investigated the levels of IGF1 in acute myocardial infarction (AMI) and sought to determine whether a decrease might influence the long-term prognosis.

Material and methods
Sixty-five patients who were admitted to our hospital with AMI were included in the study along with 26 other patients without coronary artery disease (CAD) who served as the control group. Fasting blood samples of all patients and CAD were obtained at the hospital and ~10 months later in order to evaluate their IGF1 and IGF-binding protein 3 (IGFBP3) levels.

Results
In the patients with AMI, the IGF1 levels were higher than in the control group ($P$=0.002). At the 10th month, the levels of IGFBP3 were significantly higher, and the IGF1 levels were higher but were not more significant than those in the control group ($P$=0.006 and $P$=0.05 respectively). When we compared the 10-month and baseline values, the levels of IGFBP3 were significantly higher at 10 months. In addition, the IGF1 levels were lower but did not achieve significance at 10 months ($P$=0.04) or at the time baseline measurements were taken ($P$=0.06). Furthermore, no significant differences were found between the patients with low or high IGF1 and IGFBP3 levels at the two different time periods when they were compared in terms of cardiac events.

Conclusion
At the 10-month follow-up after AMI, the serum total IGF1 and IGFBP3 levels were still high, and no correlations existed between the IGF1 and IGFBP3 levels and cardiac events.

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EP613
Association between the transient receptor potential channel gene polymorphisms and metabolic syndrome
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Introduction
Metabolic syndrome (MetS) is characterised by a combination of visceral obesity, hypertension, insulin resistance, dyslipidemia, and impaired glucose tolerance. It is a prominent risk factor for cardiovascular morbidity and mortality. The etiology of MetS is complex. The progression of MetS is influenced by genetic susceptibility and environmental factors. The aim of this study was to investigate a possible association between transient receptor potential potential (TRP) channels gene polymorphisms and MetS in a Turkish population.

Methods
A total of 142 patients with obesity-related MetS and 166 healthy controls with similar age and sex were enrolled to this study. Genomic DNA from the participants was analyzed by a BioMark 96.96 dynamic array system (Fluidigm, South San Francisco, CA, USA). For calculation of the significance of differences in genotype and allele frequencies, the $χ^2$ test or Fisher’s exact test was used. A $P$ value of <0.002 (0.05/25) was considered statistically significant after Bonferroni’s correction for multiple testing.

Results
There was an increase in A allele (64.6% in patients vs 49.5% in controls) and decrease in G allele frequencies (35.4% in patients vs 50.5% in control, $P$=0.0019) of the TRPM5 gene rs4929982 (Arg578Gln) polymorphism. We also observed that the distribution of genotype and allele frequencies of the TRPM5 gene rs12472151 in MetS patients were significantly different from controls ($P$<0.0001). However, no associations were found with the other 23 polymorphisms studied.

Conclusion
In conclusion, to the best of our knowledge, the present case–control study is the first to examine the potential involvement of TRP channel gene variations in the risk of incident MetS. Our data showed that genetic polymorphisms in TRPM5 and TRPM8 genes may modify individual susceptibility to MetS in the Turkish population.

Disclosure
This study was supported by a project (TF.13.20) from the University of Gaziantep.

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EP614
Effects of omega-3 fatty acid on pre- and post-prandial triglyceride and metabolic parameters with standard meals in patients with hypertriglyceridemia: open, multicentre study
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Introduction
We evaluated the effects of dietary supplementation of omega-3 (3F) fatty acid on post- and post-prandial triglyceride and metabolic parameters with standard meals in patients with hypertriglyceridemia.
Introduction
Nonfasting duration is much longer than fasting time in a day. Although there is a few reports on the importance of postprandial triacylglycerol (TG) on cardiovascular outcome, TG variation after meal is one of main obstacle of clinical trial. The purpose of this study is to determine effects of a 6-week period of omega-3 fatty acid supplementation on fasting and postprandial TG and metabolic parameters in response to standard test meals.

Methods
The study population included 26 patients with hyperglycemia (≥200 mg/dl). They were educated and randomly allocated to treatment group by omega-3 fatty acid supplementation (Omnicor, 2 g/day) or control group, and followed-up for 6 weeks in three hospitals. At days 1 and 42 visit, fasting and postprandial TG data were obtained respectively, before and after standard meals with 710 kcal.

Results
In intragroup analysis, treatment group with omega-3 fatty acids showed significant decrease on fasting TG (235.2 mg/dl vs 254.2 mg/dl, P < 0.046) and especially post-prandial TG (357.3 mg/dl vs 272.7 mg/dl, P < 0.033), while control group showed no significant difference during follow-up (271.2 mg/dl vs 255.1 mg/dl, P > 0.790 for fasting TG and 343.7 mg/dl vs 324.7 mg/dl for post-prandial TG). However, in intergroup analysis, there was no significant difference between two groups in fasting and post-prandial TG (% change: P = 0.287 and 0.303 respectively). There was no significant improvement in other lipid profiles. No significant adverse events were registered during this study.

Conclusion
The omega-3 fatty acids achieved a significant reduction of fasting and post-prandial triglycerides without adverse reactions. Because the trend of improvement in post-prandial TG appeared in the treatment group than control group, further study including more subjects will be needed.

Disclosure
This study was supported by Gun-il Pharmacy, Seoul, Korea.

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EP616
A low glycemic index, low glycemic load snack based on stevia and fortified with vitamin D, improves metabolic/hormonal profile, and compliance in normal subjects and prediabetics; results from a 4 months, controlled trial
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Introduction
Half of subjects following a low-calorie dietary program cannot tolerate its nutritional restrictions and abandon it. A realistic approach to overcome this obstacle is the addition of low glycemic index (GI), low glycemic load (GL) snacks in their nutrition. Stevia, a potent, low calorie sweetener exerts anti-hyperglycaemic and insulinotrophic activities. Furthermore, Vitamin D deficiency may affect diabetes development in the long run.

Aim
To assess a new bioactive, low GI/ low GL product, based on stevia glycosides and fortified with vitamins A and D, regarding metabolic/hormonal profile and the compliance of subjects undergoing a hypocaloric nutritional approach.

Methods
A 4-month controlled, prospective trial in healthy subjects (n = 80) and prediabetics (n = 39). 119 overweight/obese subjects were enrolled and given the same hypocaloric nutritional approach and the choice of either a stevia snack consumption (4/week, n = 60) or the consumption of a personal choice dessert (1/week, n = 59).

Results
In all groups, a significant weight loss was observed (P < 0.05). In healthy subjects waist circumference, insulin, and HOMA index were significantly improved, irrespectively of the method of intervention (P < 0.05). In prediabetics, insulin, Hba1c, HOMA index, CRP, and vitamin D levels were ameliorated only in the stevia group. The attrition rate was similar between groups (~8%), but the majority of the stevia group suggested that they preferred this approach.

Conclusions
The consumption of low GI, low GL snacks based on stevia and fortified with vitamin D, increases compliance in subjects following a nutritional programme and exerts a beneficial role on the metabolic/hormonal profile of people with prediabetes.

Disclosure
This work was supported by the Greek and Chinese General Secretariat for Research and Technology (grant number: 12CHN156).

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EP617
Intima–media thickness measurement of the carotid artery in patients with primary hyperparathyroidism
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Aim
The intima–media thickness (IMT) measurement of the common carotid artery is recognised as an important marker of systemic atherosclerosis. It may be useful in

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predicting the cardiovascular events, since it is related to the severity of coronary artery disease. The aims of this study were to analyse whether correlations exist between the IMT of the common carotid artery and the main clinical and biochemical parameters in patients with primary hyperparathyroidism (PHPT). Patients and methods Thirty patients with biochemically confirmed PHPT (group A, cases), 26 patients (group B, control group who have DM and/or HT), and 24 healthy volunteers (group C, healthy controls) were prospectively enrolled in the study. All patients underwent ultrasound examination and the IMT of each carotid artery were recorded. Results The final pathology showed a solitary parathyroid adenoma in all cases. Age, sex, mean IMT, and biochemical parameters, except serum calcium and PTH, did not differ significantly between groups (Table 1). But IMT is higher than case group compared to the other groups. But it was not statistically significant (P = 0.05). In group A, DM and/or HT rate was 37.5% while 32.5% in group B and 0% in group C. There was positive significant correlation between serum calcium and IMT (r = 0.32, P = 0.003). But there was no correlation between IMT and serum parathyroid hormone and or serum phosphate.

Table 1: Main clinical and biochemical parameters of groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.07 ± 12.95</td>
<td>53.85 ± 5.98</td>
<td>47.75 ± 6.08</td>
<td>0.05</td>
</tr>
<tr>
<td>Sex (female/ male) (n)</td>
<td>24/6</td>
<td>24/2</td>
<td>20/4</td>
<td>0.421</td>
</tr>
<tr>
<td>Ca (mg/dl)</td>
<td>11.45 ± 1.04</td>
<td>8.88 ± 0.44</td>
<td>9.02 ± 0.43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P (mg/dl)</td>
<td>2.76 ± 0.48</td>
<td>2.96 ± 0.16</td>
<td>2.94 ± 0.13</td>
<td>0.05</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>229.98 ± 182.84</td>
<td>41.38 ± 3.62</td>
<td>42.87 ± 2.67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IMT (mm)</td>
<td>0.83 ± 0.14</td>
<td>0.76 ± 0.19</td>
<td>0.72 ± 0.51</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Group A: cases; group B, controls with DM and/or HT; group C, healthy controls; PTH, parathyroid hormone; IMT, intima–media thickness of the common carotid artery.

Conclusion Several cardiovascular risk factors have been reported in patients with PHPT since both calcium and PTH are related to heart function. Our results suggest that hypercalcaemia may represent a risk of carotid atherosclerosis in patients with PHPT.

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EP619
Steroid hormones related to 11β-hydroxysteroid dehydrogenase in obese adolescents and non-obese controls
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Introduction Elevated activity and expression of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) are associated with the development of obesity and metabolic syndrome. This enzyme is responsible for majority of the extra-adrenal production of glucocorticoids. It regulates active cortisol from biologically inactive cortisone. Human 11β-HSD1 also reversibly catalyzes the inter-conversion of 7α-hydroxy- and 7β-hydroxy-DHEA into 7-oxo-DHEA. In order to examine the role of 11β-HSD1 in human obesity, we followed the circulating levels of steroids related to 11β-HSD1 in obese patients and non-obese controls.

Methods/design The cohort of 282 obese adolescents, 154 girls (median age 15.31, range 14.17–16.68 years) and 128 boys (median age 14.95, range 13.87–16.16 years), BMI > 90th percentile and the cohort of 100 nonobese controls including 50 girls (median age 15.29, range 14.32–16.79 years) and 50 boys (median age 15.29, range 14.47–16.77 years), BMI 25th–75th percentiles were examined. Circulating levels of cortisol, cortisone, DHEA, 7-oxo-, 7β-hydroxy-, 7α-hydroxy-, and 16α-hydroxy-DHEA were analysed by liquid chromatography-tandem mass spectrometry method.

Results We found significantly increased levels of cortisone in obese subjects, while cortisol levels did not differ between obese and nonobese adolescents. Higher circulating levels of DHEA in obese girls, higher 7β-hydroxy-DHEA in both sexes, higher 7-oxo-DHEA in obese boys and reduced levels of 16α-hydroxy-DHEA in obese girls were observed. While the absolute levels of circulating 7α-hydroxy-DHEA did not differ between examined groups, the 7α-hydroxy-DHEA/DHEA ratio was significantly lower in obese subjects suggesting reduced 7α-hydroxylatation in obesity.

Conclusion Our findings support a role of 11β-HSD1 as well as derivatives of DHEA in the control of human metabolism.

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EP620
Liraglutide improves surfactant protein-B production and reduces right ventricular hypertrophy in a rat model of interstitial pulmonary fibrosis
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Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive and fatal lung disease characterized by excessive matrix deposition that disrupts the normal alveolar architecture and lung physiology. Glucagon-like peptide 1 (GLP1) receptor is expressed in the lung where it is implicated in the synthesis of the protein (SPs) and lipid fractions of the surfactant. We have previously shown that the GLP1 receptor agonist, liraglutide (LIR), is able to restore surfactant protein-B (SP-B, a limiting factor for survival) production and right ventricular hypertrophy in streptozotocin-diabetic rats. The aim of this work was to study the effects of the GLP-1 receptor agonist liraglutide in the production of SPs, fibrosis indicators and right ventricle mass in a rat model of IPF. IPF was induced in rats by the single intra-thoracic instillation of bleomycin (BLM, 2.5 mg/kg). From day 10 rats were treated with liraglutide (100 µg/kg per 12 h s.c.), once overwhelmed the acute inflammatory phase, and then they were sacrificed in day 21. Heart ventricles and lungs were isolated, weighted, and frozen. The expression levels of SP-B, thyroid...
transcription factor 1 (TTF1, a transcription factor for SP-B) and receptors for GLP1 and leptin were lower in lungs of BLM-treated rats; but their levels were restored by liraglutide treatment. The right ventricle weight was also augmented in BLM-treated rats and liraglutide administration partially restored right ventricle masses. We have also measured the expression levels of lung fibrosis indicators as collagen type-Iα1 and connective tissue growth factor (CTGF), which yielded higher levels in BLM-treated animals, but liraglutide did not modify those. In conclusion, we found that liraglutide was able to increasing pulmonary SP-B and partially reverse right ventricular hypertrophy associated to the lung fibrosis induced by BLM, however, it can’t improve the interstitial fibrosis once consolidated.

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EP621
Metabolic syndrome and muscle mass
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Objective
Low skeletal muscle mass is an emerging risk factor for metabolic disorders. In this study, we aimed to evaluate the relationships between fat mass, muscle mass, muscle fat mass ratio, total fat mass, and abdominal fat mass ratio by comparing the body compositions in obese women with and without metabolic syndrome.

Methods
Totally 89 obese women (mean±s.d., age 42.1±12 years, BMI 36.5±4.2%) with newly diagnosed metabolic syndrome (MS, n=64, case group) and without metabolic syndrome (NMS, n=25, control group) were included into study. Body composition was measured by bioelectrical impedance analysis (BIA). Metabolic syndrome was defined using the International Diabetes Federation 2005 diagnostic criteria.

Results
It was found that subjects with MS had 57.2±13.2 kg muscle mass, 41.2±8.9 kg of fat mass. Their muscle/fat ratio was 1.46±0.49 and total fat/abdominal fat ratio was 1.99±0.25. Subjects without MS had 53.5±8.4 kg of muscle mass 39.2±9.3 kg of fat mass. Their muscle/fat ratio was 1.44±0.42 and total fat/abdominal fat ratio was 1.96±0.37 and there was no statistical significant difference (P>0.05). On the other hand subjects who had MS and non-MS, fasting serum insulin and HOMA-IR values were 21.1±11.8 and 11.3±5.5 μU/ml; 5.5±3.5 and 2.7±1.5 μU/ml respectively (P<0.01).

Conclusion
There is evidence that reduction in muscle mass and muscle/fat ratio is a risk factor for metabolic syndrome, but we did not find any significant reduction of muscle mass in subjects with MS in this study. This study should be redesigned in larger population to evaluate the meaning of these results. This may be explained by the anabolic effect of increased serum insulin levels in metabolic syndrome patients.

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EP622
Increased FNDC5 (irisin) expression in subcutaneous adipose tissue in obese patients with type 2 diabetes 1 year after bariatric surgery
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Aim
Gastric bypass surgery improves glycaemic control, but the underlying mechanisms including potential changes in adipocytokine axis are incompletely understood. The aim of this study was to investigate potentially causal or associated alterations in gene expression of adipokines, myokines, and hormones in the subcutaneous and visceral adipose tissue of diabetic and non-diabetic obese subjects before and after gastric bypass.

Material and methods
Biopsy specimens from the subcutaneous adipose tissue of 12 diabetic and 12 non-diabetic patients at and 1 year after gastric bypass were analysed with quantitative real-time PCR for the expression levels of various adipokines, myokines, and hormones such as adiponectin, leptin, irisin (FNDC5), osteocalcin, and osteopontin.

Results
Non-diabetic subjects were found to express significantly higher levels of FNDC5 in the subcutaneous adipose tissue than diabetic subjects before gastric bypass (P=0.0167). FNDC5 expression in the subcutaneous adipose tissue of diabetic patients was significantly increased one year after surgery (P<0.001). In non-diabetic subjects, there was no significant increase observable (P=0.158). The increase in FNDC5 in diabetic subjects correlated with reduction in BMI (Pearson’s r=0.718, P=0.009). No correlation was observed between FNDC5 expression and early insulin response or insulin sensitivity index.

Conclusion
To our knowledge, this is the first study to investigate the role of the novel myokine irisin in bariatric surgery mediated weight loss. The results of this study demonstrate that exercise-independent weight loss increases irisin expression levels in subcutaneous adipose tissue of diabetic subjects.

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EP623
Relationship between TSH and cortisol levels in euthyroid obese subjects
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Aim
Several studies have reported that TSH is positively correlated with obesity, dyslipidaemia, and impaired glucose metabolism even in normal range limits. We aimed to evaluate the TSH levels in a cohort of otherwise healthy obese women without clinical evidence of thyroid dysfunction.

Materials and methods
127 female patients were enrolled in this study. Anthropometric and laboratory measurements were retrospectively analysed. Patients were divided into subgroups according to BMIs.

Results
Groups were age-matched. No statistically significant correlation was found between TSH and BMI, HOMA-IR, triglyceride, HDL, or LDL values. But a significant positive correlation between TSH and cortisol levels was revealed (P=0.000). As expected, HOMA-IR and triglyceride values were positively, HDL levels were negatively correlated with BMI (P<0.05).

Conclusion
In our euthyroid cohort, we did not find any significant association between plasma TSH levels and obesity. However, the positive relationship between TSH and cortisol is a compelling finding. It’s known that overt hypothyroidism is associated with frankly elevated cortisol levels. But our study finding suggested a correlation within normal range limits and requires further investigations in order to better understand the mechanisms involved in the TSH-cortisol relationship.

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Diabetes is associated with a greatly increased risk of cardiovascular disease and the advanced glycation end products (AGEs) and their receptors play an important role in these complications.

Objective
To study the association between AGEs and sRAGE levels with cardiovascular risk factors in obese and non-obese newly diagnosed type 2 diabetic patients.

Material and methods
We conducted a cross-sectional study in subjects with type 2 diabetes mellitus of recent diagnosis, by means of a glucose tolerance test according to the ADA criteria (age 35–65). We studied two groups, one with obesity (n=40) and other with normal weight (n=40). We measured somatometrical variables, BMI, DBP, glucose, HbA1c, lipid profile, insulin, HOMA-IR, serum AGEs, ICAM-1, VCAM-1, 8-oxo-DG, MDA, and sRAGE. We also measured carotid intima–media thickness (cIMT) and flow-mediated dilation (FMD) by ultrasonography.

Results
The study population was composed of 80 patients with average age: 48 ± 7.3 years old and HbA1c: 6.53 ± 1.08. Serum AGEs (P < 0.0001), sRAGE (P < 0.0001), ICAM-1 (P < 0.0001), VCAM-1 (P < 0.0001), 8-oxo-DG (P < 0.0001), MDA (P < 0.0001), HOMA-IR (P < 0.0001), and cIMT (P < 0.001), were lower in the non-obese than in obese patients, while FMD (P < 0.02) was higher in the obesity group. In the total group serum AGEs was associated with age (P < 0.02), ICAM-1 (P < 0.0001), and HOMA-IR (P < 0.01); in the obesity group, sAGEs were associated with age (P < 0.01), HbA1c (P < 0.01), HOMA-IR (P < 0.0001), and in the normal weight subjects with FMD (P < 0.001). In the total group sRAGE were associated with VCAM-1 (P < 0.0001), ICAM-1 (P < 0.0001), MDA (P < 0.0001), and cIMT (P < 0.001); in the obesity group with HbA1c (P < 0.02), VCAM-1 (P < 0.02), MDA (P < 0.0001), and 8-oxo-DG (P < 0.0001).

Conclusion
The results show association of serum AGEs with ICAM-1 and HOMA-IR and strong association of sRAGE with VCAM-1, ICAM-1, MDA, and cIMT.

Disclosure
Supported by Grant of FOMIX-GTO (GTO-2012-C03-195211).

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**EP625**

**The body distribution of iodine-125 labeled irisin in 10-week-old rats: preliminary data**

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Introduction
Irisin is a newly discovered adipokine, that has a significant influence on body metabolism. Available data about this peptide is still insufficient. The aim of the study is to provide some initial information about body distribution of irisin in rats.

Methods
The studied group consisted of 27 10-week-old female Wistar rats, which received intraperitoneally 0.7 µCi of iodine-125 labeled irisin. The studied rats were divided into four subgroups: six were decapitated after 15 min, five after 30 min, 1 h and 2.5 h and last six after 5 h. The samples from blood, kidneys, liver, subcutaneous and visceral fat, heart, skeletal muscles, diaphragm, adrenals, brain and cerebellum were taken, scaled and the radiation was measured (counts per minute (CPM)). The same procedure was applied for five rats which received only saline intraperitoneally – control group.

Results
The maximum radiation (CPM/I g) in the blood was registered 1 h after the injection. At that moment the highest radiation was detected in kidneys. After 1 h the maximum radiation was registered also in liver, heart, and skeletal muscles. In case of brain and cerebellum the maximum point was depicted after 2.5 h.

**Conclusions**

The diaphragm, subcutaneous fat, visceral fat, and adrenals presented very high radiation just after the injection, which decreased rapidly with time. At every point of the study the studied group tissue radiation was significantly higher than in the control group (P < 0.05).

The place of injection, thus is not reliable.

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**EP626**

**Obesity and breast cancer – does size matter?**

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Introduction
The epidemic of obesity has risen many health concerns, beneath the metabolic syndrome. One of these problems is the effect of obesity on cancer evolution. Populational studies have shown a direct correlation of BMI with worse prognostic, life quality and occurrence of comorbidities in neoplastic diseases, one of the most studied being breast cancer.

Patients and methods
We retrospectively analysed the evolution of postmenopausal obese and overweight women with non-metastatic breast cancer with antiestrogen treatment (selective oestrogen receptor modulators and/or aromatase inhibitors). From the 235 patients who received this treatment we selected 62 with regular records of BMI. Excluding criteria were previous hormonal treatment of menopause, diabetes mellitus at the diagnosis, and smoking. Mean age at the diagnosis was 57.5 ± 12 years, mean BMI 28.5 ± 4.6 kg/m2. Survival was between 3 months and 20 years.

Results
Pearson correlation showed a negative correlation between BMI and survival time (r = -0.357, P = 0.04), however, there were no statistical differences between normal (N), overweight (OW), and obese (O) women respectively (t-test N vs OW P = 0.33, N vs O P = 0.41, OW vs O P = 0.46). No modifications of life style could be noticed, at least in the OW and O women, since their weight remained practically unchanged. Women with longer survival were included in a quality of life study and, also all had a slight deterioration of role functions, emotional and cognitive functions, no differences associated with higher BMI could be observed.

Conclusion
Breast cancer is a multifactorial disease. Obesity is considered a predisposing factor, especially in postmenopausal women. However, many studies showed that not the obesity per se but that associated with sarcopenia has a most deleterious effect. Our study is limited by its retrospective design and the absence of body composition evaluation but had demonstrated direct association between obesity and a poor survival rate.

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**EP627**

**Irisin:leptin ratio, a biological marker of lean/fat mass, may help to identify LMNA-mutated familial partial lipodystrophies**

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Irisin is a myokine correlated with lean body mass, despite its association with cardiovascular events (Mantzoros 2014). Increased muscle volume and

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lipodystrophy have been reported in female FPLD (J CECM 214). Our aim was to determine whether irisin could help to distinguish certain lipodystrophic obese from FPLD.

Methods and patients
Circulating irisin levels (ELIA Phoenix) were measured in 20 LMA-related FPLD, 19 normal-weighted controls (H) and 13 obese non-diabetic (OND) patients, and correlated with body composition (DEXA/MRI), and metabolic and inflammatory (CRP, leukocytes CD4) parameters (Clin.gov 2009-A01169-48).

Results
Irisin medians differed between the three groups (P: 0.0076) and were higher in OND (P: 0.0099) and FPLD (P: 0.047) than in H groups, without difference between FPLD and OND. Irisinemia, similar between male and female, was positively correlated to lean mass (g/height^2 (r=0.51; P<0.0001), BMI, triglycerides (r=0.45–0.49; P<0.001) and to a lesser extent to insulin, body weight, MRI-intra-abdominal fat mass, MRI-intra-abdominal/MRI-total fat mass, FBG, Alc, cholesterol, and ASAT (r=0.42–0.33; P<0.001). The ratio “lean mass/height^2” differed significantly between the three groups (P<0.0001) with higher values in OND (P<0.0001) and FPLD (P=0.03) compared to H groups, without difference between FPLD and OND. Leptinaemia was higher in OND compared to H and FPLD (P<0.0001), without difference between these two groups. The ratio “irisin/leptin” differed between the three groups (P<0.0001) with higher values in FPLD and H (both P<0.0001) compared to OND, without difference between FPLD and H. Irisin was not correlated with leptin and inflammatory parameters.

Conclusion
FPLD is characterized by high irisinemia and low leptinaemia, OND by both high leptinaemia and irisinemia. Irisin is increased in diseases characterised by higher lean mass whatever the amount of fat mass. Irisin/leptin ratio, a biological marker of lean/fat mass, may help to identify FPLD.

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EP629
IGF-1 levels correlate with T₄ status in chronic heart failure outpatients: preliminary data
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Background
A variety of hormones may be down-regulated in CHF patients. Impaired activity of the GH/IGF-1 axis has been described and is associated with poor clinical status and outcome. Moreover, a decrease in serum T₄ is correlated to the severity of the heart disease as assessed by the NYHA classification. Aim of this study was to evaluate a possible correlation between IGF-1 levels and T₄ status in a cohort of CHF outpatients.

Materials and methods
Forty-eight consecutive CHF outpatients (79% males; age 61±13 years; BMI 29±5 kg/m²; NYHA class 2.3±0.6; 47% with ischemic disease), in stable clinical conditions from at least 30 days, in conventional electrical and medical therapy (87% taking ACE-inhibitors or angiotensin receptor blockers, 96% ß blockers, 96% diuretics, 72% anti-aldosterone drugs, 13% digitalis, 14% nitrates), were enrolled in the study. They were submitted to physical examination, electrocardiography and echocardiography. Blood samples were drawn to assess renal function, Na⁺, haemoglobin, NT-proBNP, T₃, T₄, TSH, IGF-1, testosterone, DHEA and insulin levels.

Results
At univariate analysis, IGF-1 showed a direct correlation with fT₃ and the same was found between IGF-1 levels and fT₃/fT₄ ratio, whereas no correlation was found between IGF-1 and the other measures. Furthermore, at multivariate analysis, including also NYHA class, fT₃ was the only independent predictor of IGF-1 levels. The figure below shows a direct correlation between IGF-1 levels and both fT₃ and fT₄ levels. The conclusion resulted from the IGF-1 levels and fT₃/fT₄ ratio.

Conclusions
Impaired IGF-1 and fT₃ status may both represent a derangement strictly correlated to the severity of the clinical condition in CHF.

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EP630
Diet relationship with the metabolic syndrome’s elements
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Background
Diet modification is an important part of the metabolic syndrome’s management but there is limited data regarding a direct relationship between food groups and the metabolic profile.

Aim
Evaluation of the influence of food groups on the elements of metabolic syndrome in a group of subjects with abdominal obesity.

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Material and methods
A cross sectional study was conducted in the Endocrinology Outpatient Clinic between February 2013 and April 2014. A sample of 290 subjects was analysed. Inclusion criteria: abdominal obesity defined according to IDF definition. Exclusion criteria: treatment for the metabolic syndrome’s elements. Variables: age, sex, environment, waist, BMI, blood pressure, blood glucose, triglycerides, HDL cholesterol, food pyramid.

Method
Anthropometric evaluation, fasting blood sample, blood pressure measurement, food pyramid constructed based on an adapted food frequency questionnaire with 126 items analyzed with a web-based application especially developed. Statistical analysis used GraphPad Prism v. 5 and SPSS v17 with a level of significance α=0.05.

Results
Mean age was 50.6 ± 13.1 years with a sex distribution F:M 6.8:1 with the majority of subjects coming from urban areas (68.27%). In multiple regression analysis, the food pyramid elements explain 6.26% of the triglycerides variation (P=0.02), 3.14% of the HDL cholesterol (P=0.31), 4.55% of the blood glucose (P=0.09), 7.25% of the blood pressure value (P=0.08) and 5.75% of the waist circumference (P=0.01). All of the metabolic syndrome elements are correlated with waist circumference and significantly influence each other’s variability.

Conclusion
The main food groups explain a small percentage of the metabolic syndrome’s elements underlying the need for a more detailed dietary evaluation to define specific patterns associated with increased cardio-vascular risk.

Disclosure
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EP632
The relationship between haemoglobin and BMI in overweight and obese patients
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Introduction
Both overweight/obesity and central obesity were inversely associated with anemia in the studies. In our study, we aimed to determine the relationship between different haemoglobin (Hb) levels and BMI.

Materials and methods
A total of 146 patients (131 (89.1%) female and 15 (10.2%) male) were enrolled in this study. Patients were divided into five groups namely group-1 (Hb ≤ 7 g/dl), group-2 (7 g/dl < Hb ≤ 10 g/dl), group-3 (10 g/dl < Hb ≤ 12 g/dl), group-4 (12 g/dl < Hb ≤ 14 g/dl) and group-5 (14 g/dl < Hb). Complete blood count, BMI, biochemical parameters, iron and iron binding capacity (IBC), ferritin, vitamin B12 and folic acid levels of all patients were measured.

Results
BMI levels were found to be significantly different in each five groups. These differences were found between group-1 and 3 (P=0.0001), group-2 and 3 (P=0.0001), group-3 and 4 (P=0.011) and group-3 and 5 (P=0.032). A positive correlation was found between BMI and Hb (r=0.199, P=0.017). There was a positive correlation between BMI and mean corpuscular volume (MCV) (r=0.298, P=0.001), negative correlation between BMI and IBC (r=-0.223, P=0.011).

Conclusion
In obese patients, adverse effects on quality of life, exercise capacity and cardiovascular diseases of the anemia should be considered while planning lifestyle changes in obesity.

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EP631
A common variant (rs9939609) in the fat mass and obesity associated gene is not associated with obesity, but associated with metabolic syndrome in girls among adolescents
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Introduction
Fat mass and obesity associated (FTO) gene was the first susceptibility locus for obesity identified by genome wide association studies. The association of the FTO gene with obesity and metabolic syndrome is conflicting in both adults and adolescents. The aim of this study was to examine the role of the FTO gene variant rs9939609 as a candidate gene for obesity and metabolic syndrome, among Caucasian adolescents in South-eastern Turkey.

Methods
One hundred obese adolescents and 100 healthy controls were included. Obesity and metabolic syndrome criteria were defined according to the international obesity task force’s international standards and to the NCEP criteria, respectively. Rs9939609 polymorphism in FTO gene was genotyped by PCR-SNaPshot.

Results
The prevalence of metabolic syndrome was 60%. For FTO T/A polymorphism, the distribution of T/T, T/A, and A/A genotypes were 32.0, 48.0 and 20.0% in obese children compared with 41.0, 36.0 and 23.0% in controls (P>0.05). The allele frequency of T and A was 56.0, 44.0% in patients compared with 59.0, 41.0% in controls (P=0.306). There was no significant difference in genotype and allele frequencies between obese patients and controls. Also, the distribution of genotypes and alleles was not different in patients with and without MetS. However, the prevalence of metabolic syndrome in female patients with A allele carriers was more frequent than with non-carriers (carriers: 23/36, 63.9%; non-carriers: 4/14, 28.6%; χ² = 5.062; P=0.024).

Conclusion
We could not confirm the FTO rs9939609 variant as an obesity and metabolic syndrome susceptibility gene in adolescents, but we observe an association with metabolic syndrome in girls. There is a need to explain the possible gender effect of FTO gene polymorphism.

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EP633
Advanced glycation end products, their receptors RAGE and AGER-1 and their association with insulin resistance and inflammation in obese and non-obese young subjects
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In obesity the combined effects of enhanced food consumption, enhanced oxidative stress and inﬂammation could increase levels of advanced glycation end products (AGEs) and the action of their receptors.

Objective
To study circulating levels of AGEs, soluble RAGE and AGER-1 and their association with insulin resistance and inﬂammation in young subjects with obesity and normal weight.

Material and methods
We conducted a cross-sectional study in obese Young (n=80) and normal weight (n=80). We calculated the BMI according to Cole et al., and the consumption of AGEs in the diet (dAGEs) with the tables of Uribarri et al. We measured glucose, lipid proﬁle, insulin, HOMA-IR, TNF-α, serum AGEs (CML) and sRAGE. In a subsample of 27 subjects with normal weight and 21 subject with obesity we also measured the expression of RAGE and AGER1 by qPCR.

Results
We studied a total of 160 subjects (16 ± 1 years old) and 55% females. The group with obesity show higher levels of triglycerides (P<0.003), insulin (P<0.001), HOMA-IR (P<0.001) and TNF-α (P<0.04). In the groups with obesity and consumption of AGEs >9000 KU/day we found higher levels of insulin (P<0.0001), HOMA-IR (P<0.01) and sRAGE (P<0.04). CML was associated with HOMA-IR (P<0.02) and TNF-α (P<0.03). In the sample we were studied the expression of cellular receptors we found higher expression of AGER1 in the obesity group (P<0.02) and association of AGER1 with weight (P<0.02) and dAGE (P<0.02) and RAGE with physical activity (r=0.14; P<0.05).

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Conclusions
The results show higher insulin resistance and inflammation in the subjects with obesity, also association of CML with insulin resistance and TNF-α, and higher expression of AGER1 in the obesity group.

Disclosure
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EP634
Bone and calcium markers in relation to cardiovascular risk in patients with osteoporosis
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Aim of the study was to evaluate the relationship between biochemical bone turnover markers, calcium homeostasis parameters and the cardiovascular risk in patients with osteoporosis.

Materials and methods
Subjects were 246 patients (mean age of 56.64) diagnosed with osteoporosis referred to the endocrine department of Elias Hospital, between 2009 and 2013, and who agreed with the terms of the study. Data collection consisted of clinical evaluation, physical exam and biochemical routine blood tests and hormones and the parameters of calcium homeostasis needed for differential diagnosis of osteoporosis. Osteoporosis was diagnosed based on the WHO criteria and metabolic syndrome based on the IDF 2007 guidelines. In order to evaluate the relationship between calcium and bone parameters and cardiovascular risk, we used metabolic syndrome as the criteria to segregate the subjects in control group (without Mets) and study subjects (with Mets).

Results
Serum intact PTH levels were significantly higher in Mets group: 76.2 (40.8) pg/ml, comparing to 65.6 (42.8) pg/ml in control group (P<0.01). No other calcium or bone biochemical marker (serum calcium, 24 h calcuria, serum osteocalcin, 25HO vitamin D, serum betacrosslaps) was significantly different across the study groups.

Conclusion
Hyperparathyroidism, either secondary or primary is frequent among patients with osteoporosis. Increased level of parathyroid hormone was found to be associated with increased risk in cardiovascular disease in our patients with osteoporosis suggesting that, beside the bone aspects, there may be also some other metabolic effects of the excess of the parathyroid hormone.

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EP635
Therapeutic education contributes to minimise excess weight in Prader-Willi syndrome
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Introduction
Prader-Willi syndrome (PWS) is a complex genetic disorder characterised by hyperphagia with progressive obesity, dysmorphic features, hypotonia, mental retardation, behavioural abnormalities and endocrine dysfunctions as hypogonadism and growth hormone (GH) deficiency. PWS is the most commonly identified genetic cause of obesity.

Methods
We reviewed five cases of confirmed PWS (three female and two male patients, aged between 8 and 32 years old) evaluated at the Endocrinology Department of Iasi between January 2008 and July 2013. Clinical and hormonal data were documented.

Results
All patients had specific clinical features of PWS and genetic confirmation. They were all born in non-sanguine couples, four of them with low birth weight. After the first year of life they presented hyperphagia with rapid and important weight gain, except for one case where hyperphagia began in adolescence (at 13 years of age). The major weight gain was until late adolescence (> +6 s.d.). Nutritional counselling, with detailed information about diet, exercise, and subsequent adverse consequences of obesity, was offered to patients and family in order to ameliorate their eating behaviour. After that, the three patients that reached adulthood achieved a mean weight at +1.5 s.d. (under rigorous alimentation). Paradoxically, all patients had a higher height than expected (mean +1.5 s.d.) in childhood and adolescence, even though three of them had low IGFI. Two patients had their first endocrinological examination in adulthood and presented a satisfactory final height (>155 cm).

Conclusions
Therapeutical education of the family, performed as early as possible, is an important determinant of the disease evolution and diminishes the potential weight gain. Although most patients with PWS have morbid obesity it seems that caregivers involvement in weight management may lead to favorable results.

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EP636
The use of intermittent 7.5 mg tolvaptan on an out-patient basis for SIADH: a retrospective audit from a tertiary cancer hospital
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Tolvaptan (a V2 receptor antagonist) is licensed for correction of hyponatraemia in patients with SIADH at an initial dose of 15 mg od. Data in oncology patients with SIADH suggest 7.5 mg can safely and effectively increase sodium levels where 15 mg can on occasion lead to too rapid a correction. Recommendations suggest a repeat sodium taken at 4–6 h. We retrospectively assessed the safety and efficacy of intermittent out-patient dosing with 7.5 mg tolvaptan. Pharmacy records and casenotes were interrogated to find all patients given out-patient prescriptions for tolvaptan between April 12 and January 15. 15 doses were administered in a total of four patients (three men, one female; mean age 63 years). All had biochemically confirmed SIADH secondary to small cell lung cancer, had received fluid restriction and demeclocycline prior to tolvaptan as inpatients and were euvoalamic. All patients were also receiving therapy for the primary malignancy concurrently. Indications for treatment were symptomatic hyponatraemia or downward trending sodium. Mean pre-out-patient tolvaptan sodium was 126 mmol/l (range 122–128). Mean first sodium post-tolvaptan was 133.6 mmol/l (range 128–139), with mean increase 7.6 mmol/l. Timing of repeat sodium ranged from 6 h to 6 days. On eight occasions a repeat sodium was done at 6 h – mean sodium rose from 125.75 mmol/l (range 122–128) to 132 mmol/l (128–137). The largest rise was 10 mmol/l at 6 h.

No adverse events were encountered. One patient died due to progressive malignancy. Conclusions
Outpatient use of single 7.5 mg doses of tolvaptan is effective at raising serum sodium in oncology patients with SIADH, thus potentially reducing admissions with economic (dose and bed-stay) and patient benefits. There were no adverse effects encountered in the small patient cohort analysed, but robust protocols need to be in place to prevent complications. Improvements need to be made in checking a 6-h sodium.

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EP637
Type 2 diabetes mellitus and obesity: the possibilities of antihypertensive therapy
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Purpose
To evaluate the effectiveness of a combined antihypertensive therapy in treating arterial hypertension (AH) in patients suffering from diabetes mellitus (Type 2 DM) on different stages of obesity.

Materials and methods
80 patients suffering from Type 2 DM and AH on different stages of obesity underwent a monitoring. Depending on the stage of obesity, the patients were divided into three groups. The groups were comparable by age, sex, AH stage. The patients received comparably oral hypoglycemic agents. On voluntary basis the patients did not receive anti hypertensive agents 5–7 days before being included into the research. Aiming at correcting AH, the patients received PRESTANCE (the combination of perindopril and amlopidine) in the doses of: 5/5, 10/10, 15/10 during 12 months. Daily monitoring of AP (ABPM) was conducted with the help of a non-invasive portable system, HbA1c was determined. The blood glucose was determined on an empty stomach and 2 h after meals. The treatment of results was carried out with the use of STATISTICA pack.

Results
The average age of the patients was 57.5 ± 3.4 years, women prevailed − 75%. The average ABP value was: 168 ±11 and 105 ±7 mmHg – for systolic and diastolic blood pressure respectively. By week 12 observations of 85% patients from group 1 reached the target ABP and was retained until week 48, 78% patients from group 2 reached the target values of ABP and 72% patients from group 3 retaining it until observation week 48. By week 12 of observation in each group was significantly (P < 0.01) decreased the level of total cholesterol plasma, LDL cholesterol, triglycerides, fasting and postprandial blood glucose, HbA1c and BMI showed a decrease. All the patients participating in the research, showed good tolerance of PRESTANCE.

Conclusions
The combination of perindopril and amlopidine provides sustainable management of ABP in patients with Type 2 DM and different obesity stages, is well tolerated, has a beneficial effect on carbohydrate and lipid metabolism, leads to weight decrease.

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EP638
Serum adipokine profile and adiponectin gene expression in neck adipose tissue in premenopausal and postmenopausal women
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Adipokines are an important contributor to the circulatory milieu of the body. The spectrum of adipokines changes as dysfunctional features of adipose tissue develop and the menopause is a time when an impairment of metabolic balance appears. The aim of this study was to examine several serum adipokines and adiponectin gene expression in subcutaneous and deep neck adipose tissue in women. Samples of serum, subcutaneous and deep neck adipose tissue were taken in 41 (12 premenopausal and 29 postmenopausal) women undergoing routine thyroid or vascular surgery. Serum adiponectin, leptin, omentin-1, monocyte chemoattractant protein-1 (MCP-1), fibroblast growth factor 21 (FGF21), retinal binding protein 4 (RBP4), insulin, glucose, triglycerides, HDL-cholesterol and C-reactive protein were determined. HOMA-IR was calculated and anthropometric measurements were performed. Adiponectin gene expression in adipose tissue samples was analysed by RQ-PCR method. Serum adiponectin and omentin-1 were negatively and leptin was positively associated with body weight, BMI and waist and neck circumference. RBP4 correlated with waist circumference and triglycerides. Leptin also was associated positively and omentin-1 negatively with triglycerides. FGF21 correlated with glucose and HDL-cholesterol. Omentin-1 negatively correlated with RBP4 and positively with serum adiponectin. Both serum adiponectin and omentin-1 were negatively associated with leptin. MCP-1 correlated only with RBP4. FGF21 didn’t correlate with other adipokines. Subcutaneous and deep adipokinetin gene expressions were negatively associated with insulation, HOMA-IR and RBP4 but positively with omentin-1. Comparisons between premenopausal and postmenopausal group yielded significant differences in insulin, HOMA-IR, MCP-1 and RBP4. These results confirm multiple associations of various adipokines with metabolic parameters and secretory features of the neck adipose tissue depot. However, they also suggest that some adipokines cluster in specific profiles with potential particular biologic functions that should be further elucidated.

Disclosure
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EP639
Impact of visceral adiposity on blood pressure in normotensive people: a study among health staff
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Background
Obesity is often complicated by cardiovascular and atherosclerotic disease. Central or visceral obesity is known to be associated with hypertension and cardiovascular disease. Even though BMI is a good indicator of obesity in epidemiological studies, it does not differentiate between lean and fat mass. Furthermore waist circumference (WC) and visceral fat percentages are better indicators of visceral obesity. Aim of this study was to investigate the correlation of blood pressure with different measures of obesity in normotensive people.

Method
A cross sectional study carried out among the health staff in a tertiary care setting. 452 were screened among all categories of health staff and 410 were enrolled for the study excluding the known hypertensive people. Body fat and visceral fat percentages were estimated using bioelectrical impedance analysis (BIA) method.

Results
Out of the 410 subjects 63% (n = 258) were females and 37% (n = 152) were males. Mean age of the study population was 41.7 ± 9.4 years. Mean systolic blood pressure (SBP) was 121 ± 13 mmHg among males and 118 ± 12.5 mmHg among females. Mean diastolic blood pressure (DBP) was 77.82 ± 8.9 and 75.3 ± 9.0 mmHg among males and females respectively. In females both SBP (r = 0.268, P < 0.001) and DBP (r = 0.209, P = 0.001) showed strongest correlation with WC compared to visceral fat percentage, total fat percentage and BMI. In females there was a good but less strong correlation with visceral fat percentage as well (SBP P = 0.001, DBP P = 0.017). In males both SBP (r = 0.225, P = 0.006) and DBP (r = 0.180, P = 0.029) showed strongest correlation with total body fat percentage compared to the other measures of obesity.

Conclusions
Among females both systolic and diastolic blood pressures are significantly affected by increased visceral adiposity as reflected by correlation with waist circumference and visceral fat percentage. However, among males blood pressure is not significantly affected by the visceral adiposity.

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EP640
Metabolic consequences of abdominal obesity: about 105 Algerian obese patients
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Introduction
The frequency of obesity is increasing in Algeria, insulin resistance is one of the consequences pathologic of the abdominal obesity. The purpose of this work is to study the implication of the abdominal obesity in the insulin resistance and the complications which arise by the latter.

Materials and methods
The study is realised on 105 obese (85 women and 20 men) (BMI > 30) and 55 thin (40 women and 15 men) with mean age 37.60 ± 1.18 and 31.03 ± 1.73 years respectively. Glyceremia, lipids, insulin and the leptin are analysed. The resistance and the sensibility in the insulin are estimated by the index HOMA-R and QUIKI. The obesity android was held in the criteria of the US NCEP ATP III Defines by a WHR ≥ 0.85 for women and WHR ≥ 1.00 for men.

Disclosure
The study was supported by the Ministry of Science, Education and Sports of the Republic of Croatia Grant No. 198-1980955-0953.
Results
92% sick suffer from an obesity android associated with critical insulin resistance (HOMA-IR: HOMAR-IR: 12.85 ± 1.03 vs 5.17 ± 0.86 P < 0.001; QUIKI: 0.29 ± 0.002 vs 0.31 ± 0.002; P < 0.001). Plasma cortisol and leptin were higher in obese group by 16% (P < 0.005) and 75% (P < 0.001) respectively, compared to control group. According to US NCEP ATP III obese (50%) show lipid disturbances associated to dyslipidemia and metabolic syndrome. Our results show a negative correlation between QUIKI and TT (r = –0.29 P = 0.02).
Conclusion
Abdominal obesity associated with metabolic disorders have led to a metabolic syndrome according to US NCEP-ATP III and a physiological stress which stimulated the secretion of cortisol. Despite the significant increase of leptin, known to inhibit adrenal axis. These data suggest that leptin resistance is developed in obese subjects.

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EP641
Body composition in HIV-infected patients under combined antiretroviral therapy over 5 years
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Introduction
HIV infection and combined antiretroviral therapy (cART) have been associated with lipodystrophy and changes in body composition. However, there are few studies on body composition evolution of HIV-infected patients, under cART.

Aims
To evaluate the evolution of body composition in HIV-1 infected patients under cART over 5 years.

Methods
Retrospective, observational study in a cohort of HIV-infected patients on cART. Evaluation of clinical data and body composition (total fat mass, upper-limbs fat mass, lower-limbs fat mass, trunk fat mass and fat-free mass) by DXA (whole body dual-energy X-ray absorptiometry).

Results
A total of 257 patients were evaluated, with a mean age of 45.98 (11.51) years. 63% were males. The median duration of HIV infection was 7.92 (IQR: 1.90) years and the median duration of cART was 6.61 (IQR: 3.9) years. Males had a baseline mean BMI of 24.37 (22.17–26.91) Kg/m2. Over the five years, there was a significant increase in their % of upper limbs, lower limbs, trunk and total fat mass. At baseline, women had a mean BMI of 25.33 (21.92–29.18) Kg/m2. Women showed significant decrease in their % of lower limbs fat mass and an increase in % of trunk fat mass; % of total fat mass increased during the first two years and decreased since then. No differences were found regarding fat mass ratio, in both genders. During the five years of follow-up period, men showed a decrease of total fat-free mass and increase of upper-limbs fat-free mass; significant changes were also observed in lower-limbs and trunk fat-free mass distribution. Women also showed significant changes in total, lower-limbs, upper-limbs and trunk fat-free mass during follow-up.

Conclusion
Over the 5 years, there were significant changes in body composition in HIV-infected patients on cART. Different from women, men showed a sustained increase in % of fat mass of all segments evaluated.

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EP642
Patients' expectations and post-bariatric surgery satisfaction
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Introduction
Treatment satisfaction is simultaneously a cause and consequence of the success of bariatric surgery – not only it is a reflection of the efficacy of treatment, it also enhances weight loss. A questionnaire that evaluates this variable has recently been created and validated by the authors (Post-Bariatric Surgery Satisfaction Questionnaire).

Objectives
To identify patients’ expectations regarding bariatric surgery; to identify the domains that contribute to the degree of satisfaction after bariatric surgery.

Methods
Patients submitted to bariatric surgery who presented to our Obesity Outpatient Clinic between June and December/2013 were asked to complete two questionnaires – Patients’ Expectations Questionnaire and Post-Bariatric Surgery Satisfaction Questionnaire (22 items, five-point scale – 1 = very dissatisfied, 5 – very satisfied). Demographic and clinical data were also collected.

Results
A total of 86 patients were included (67% submitted to laparoscopic gastric bypass and 33% to adjustable gastric banding); 86% female, median age 50 years (min-max =23–73), median follow-up time since surgery 37 months (min-max =1–220). Actual and idealized BMI of patients was 31.7 kg/m² and 27.7 kg/m², respectively. Actual and idealized percentage of excess BMI lost was 68.8 and 85.1%, respectively. The majority of the patients selected the items ‘reduce weight’ (98.8%), ‘improve health’ (98.8%), ‘be able to choose clothing I like’ (91.9%) and ‘improve self-esteem’ (91.9%). Patients were satisfied to very satisfied in all analyzed items (median score between 1.0 and 2.0). However, 34.9% of patients feel dissatisfied to very dissatisfied with their ‘nailed physical appearance’, and 12.8% with ‘the need of chronic medication’. 91.9% of the patients would recommend surgery to others and 90.1% of patients would undergo surgery again.

Conclusion
Patients were satisfied to very satisfied in all items tested, despite having unrealistic expectations. It is essential to assess what affects patients’ satisfaction in order to understand their behavior and optimize our intervention.

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EP643
Insulin resistance does not play a major role in lipid and apolipoprotein profile in obese women
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Background
Obesity is associated with increased atherogenesis through alterations in lipids, among other potential factors. Some of those abnormalities might be mediated by insulin resistance (IR).

Aims
To compare lipid and apolipoprotein profile between lean and obese women; to evaluate the influence of IR on lipid and apolipoprotein profile, in obese women.

Methods
We studied 112 obese and 100 normal-weight premenopausal women without known cardiovascular disease. Both groups were characterized for anthropometrics and a fasting blood sample was collected for assessment of glucose, insulin, triglycerides, cholesterol (total, LDL and HDL), and apolipoproteins A-I, A-II, B, C-II, C-III, and E; IR was assessed by the homeostatic model assessment (HOMA-IR). We compared lipid and apolipoprotein profile between lean and obese women; to evaluate the influence of IR on lipid and apolipoprotein profile, in obese women.

Results
Obese women were characterized by mean age = 34.6 ± 8.3 years, BMI = 43.6 ± 7.9 kg/m², waist circumference (Wa) = 117.5 ± 15.1 cm, and HOMA-IR = 4.28 ± 3.5. Lean women (age = 34.2 ± 8.3 years, BMI = 21.4 ± 1.7 kg/m², Wi = 71.7 ± 5.8 cm, and HOMA-IR = 1.21 ± 0.76) presented with significantly lower levels of total cholesterol (P < 0.001), LDL-cholesterol (P < 0.001), and triglycerides (P < 0.001); they presented higher levels of HDL-cholesterol (P < 0.001), Apo A-I (P < 0.001) and Apo A-II (P = 0.037). HOMA-IR showed no significant association with apolipoproteins. HOMA-IR was inversely associated with HDL-cholesterol (P = 0.048; r = −0.187) but that association disappeared when we adjusted for waist circumference. Only triglycerides were directly associated with HOMA-IR (P < 0.001; r = 0.343) independently from anthropometrics.
Conclusion
We confirm that obese women present worst lipid and apolipoprotein profile. However, with the exception for triglycerides, insulin resistance per se does not play a major role in lipid and apolipoprotein abnormalities observed in obese women.
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EP644
VEGFA expression is regulated by 17β-oestradiol and its receptors (ESR1 and ESR2) on 3T3-L1 adipocytes
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Introduction
VEGFA is considered the main angiogenic factor in adipose tissue. It is believed that a low angiogenic capacity may decrease the adipogenic potential and consequently promotes adipocyte hypertrophy, which in turn, is closely related to insulin resistance (IR). Oestradiol (E2) is a regulator of the VEGFA gene and a protector against obesity. However nothing is known about the E2 effects on VEGF adipocyte production, and its consequence for cellular sensitivity and much less about the adjacent molecular mechanisms. Thus, the aim of the present work was to investigate the role of E2 on the VEGFA expression determining the participation of the estrogen receptors ESR1 and ESR2 in this process.

Methods
Differentially treated 3T3-L1 adipocytes were treated (24 h) with 10 or 100 nmol/l of 17β-E2 and/or selective ESR1 agonist PPT, ESR1-antagonist MPP, ESR2-agonist DPN and ESR2-antagonist PHTPP. We analyzed VEGFA mRNA and protein expression by real time PCR and Western blotting, respectively.

Results
E2 enhanced VEGFA mRNA and protein (20–30%) expression at 10 and 100 nmol/l. Treatment with PPT enhanced VEGFA expression (~30%) in the absence or presence of E2. However treatment with ESR2 agonist DPN didn’t change VEGFA expression. In addition, the ESR1-antagonist MPP or the ESR2-antagonist PHTPP alone were not able to change the VEGFA expression, but in the presence of E2 the VEGFA expression was increased (20–30%) in both treatments as compared to control.

Conclusion
The present results reveal that E2 induced VEGFA production in adipocytes, in part, via activation of ESR1 receptor. However, there is evidence of co-regulation of both receptors, since in the absence of ESR1, high dose of E2 was able to induce VEGFA expression. Taken together, the increased VEGFA production induced by E2 in adipocytes can improve the local angiogenesis, protecting the adipose tissue from obesity-induced hypoxia, and consequently, from insulin resistance.

Disclosure
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EP645
Time-of-day-dependent rhythms in the transcriptional responsiveness of the rat heart to triiodothyronine
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Myocardial gene expression and metabolism fluctuate over the course of the day, in association with changes in energy supply and demand. Recently, time-of-day-dependent oscillations in myocardial processes have been linked to the intrinsic cardiomyocyte circadian clock. Triiodothyronine (T3) is an important modulator of cardiac form and function. The genomic actions of T3 are triggered after its interaction with thyroid hormone nuclear receptors that often dimerized with RXR or RORA. Some target proteins, such as PDK4, are regulated not only by the cardiomyocyte circadian clock, but also by T3, suggesting a potential interaction between the two mechanisms. Circulating levels of T3 and its intermediates exhibit a time-of-day-dependent oscillation. However, whether the sensitivity of T3 responsive tissues oscillate in a time-of-day-dependent manner is unknown. Thus, the purpose of the present study was to investigate whether the heart exhibits a diurnal variation in T3 responsiveness, at transcriptional level, and/or whether T3 impacts the circadian clock in the heart. For this, euthyroid (C) male Wistar rats were divided in two groups: vehicle or T3 (supraphysiological dose), administered 4 h prior each ZT. The animals were euthanized at the respective Zeitgeber Times, during 24 h. The hearts were excised and the mRNA expression was evaluated by RT-qPCR using Taqman probe specific for each target gene; cyclophilin was used as a housekeeping gene. One and two-way ANOVA analysis were used to evaluate the time-of-day-dependent differential expression for each gene/group and their interactions. In general, the administration of T3 promoted a marked alteration in the expression of Bma1, Pdk4 and Ucp3, revealing a time-of-day-dependent responsiveness specially at the end of the dark period for Bma1 and throughout the whole investigated period for Pdk4 and Ucp3. Our study shows that T3 might acts as a Zeitgeber, and alters the cardiac functions, which may help to explain some metabolic and functional disorders observed in thyroid diseases.

Disclosure
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EP646
Influences on post-bariatric surgery satisfaction
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Introduction
Post-bariatric surgery satisfaction relies on psychosocial and clinical factors. A questionnaire that evaluates this variable has recently been created and validated by the authors (Post-Bariatric Surgery Satisfaction Questionnaire).

Objective
To assess the relationship between treatment satisfaction and several demographic and clinical variables.

Methods
Patients submitted to bariatric surgery who presented to our Obesity Outpatient Clinic between June 2013 and December 2013 were asked to complete the Post-Bariatric Surgery Satisfaction Questionnaire (22 items, five-point scale – 1, very dissatisfied; 5, very satisfied). The percentage of excess BMI lost, the type of surgery, and patient’s age were collected.

Results
A total of 86 patients were included (67% submitted to laparoscopic gastric bypass and 33% to adjustable gastric banding); 86% females, median age 50 years (min-max = 23–73), median follow-up time since surgery 37 months (min-max = 1–220). Age, adjusted to percentage of excess BMI lost, was negatively correlated with ‘physical well-being’ (r = −0.27; P = 0.012) and with ‘enhancement of movement capabilities’ (r = −0.25; P = 0.019), but not with global satisfaction. There was no correlation between the degree of satisfaction and the follow-up time since surgery, nor differences between genders. There was a positive correlation between percentage of excess BMI lost and 15 of the items (r = 0.21–0.54; P < 0.001–0.047) and with global satisfaction (r = 0.45, P < 0.001). Patients submitted to adjustable gastric banding were less satisfied globally (P = 0.007) and in seven of the items. Results from the linear regression analysis indicate that the percentage of excess BMI lost and the type of surgery explain 29% of the variance in patients’ global satisfaction. Both variables were statistically significant, with percentage of excess BMI lost recording a higher β value (0.45 and 0.20 respectively).

Conclusion
The percentage of excess BMI lost, the type of surgery, and patient’s age influenced post-bariatric surgery satisfaction. However, these only partially explain treatment satisfaction. Other factors, namely psychosocial, are probably also involved.

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EP647
Effects of an 8-week supervised, structured lifestyle modification programme on anthropometric, metabolic, and cardiovascular risk factors in severely obese adults
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Background
Lifestyle modification is fundamental to obesity treatment, but few studies have described the effects of structured lifestyle programmes specifically in bariatric patients. We sought to describe changes in anthropometric and metabolic characteristics in a cohort of bariatric patients after participation in a nurse-led, structured lifestyle programme.

Methods
We conducted a retrospective, observational cohort study of adults with a BMI ≥40 kg/m² (or ≥35 kg/m² with significant co-morbidity) who were attending a regional bariatric service and who completed a single centre, 8-week, nurse-led multidisciplinary lifestyle modification programme. Weight, height, waist circumference, blood pressure, HbA1c, fasting glucose and lipid profiles, functional capacity (Incremental Shuttle Walk Test) and anxiety, and depression scores before and after the programme were compared in per-protocol analyses.

Results
Of 183 bariatric patients enrolled, 150 (81.9%) completed the programme. Mean age of completers was 47.9 ± 11.2 years. 34.7% were males. There were statistically significant reductions in weight (129.6 ± 25.9 kg vs 126.9 ± 26.1 kg, P < 0.001), BMI (46.3 ± 8.3 kg/m² vs 44.9 ± 9.0 kg/m², P < 0.001), waist circumference (133.0 ± 17.1 cm vs 129.3 ± 17.5 cm in women and 143.8 ± 19.0 cm vs 135.± 17.9 cm in men, both P < 0.001) as well as anxiety and depression scores before and after the programme were compared in per-protocol analyses.

Conclusions
Bariatric patients completing an eight week, nurse-led structured lifestyle programme had improved adiposity, fitness, lipid profiles, psychosocial health, blood pressure, and glycaemia. Further assessment of this programme in a pragmatic randomised controlled trial seems warranted.

Disclosure
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EP649
Prevalence of metabolic syndrome among human immunodeficiency virus and hepatitis C subjects in Southern Brazil
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Objective
To investigate the metabolic syndrome and dyslipidaemia prevalence among human immunodeficiency virus (HIV) and hepatitis C (HCV) subjects in Southern Brazil.

Methods
Cross-sectional study, including 127 subjects (n=59 HIV positive only, n=36 HIV/HCV positive, and n=32 HCV positive only) were accessed for HOME index, metabolic syndrome, and dyslipidaemias.

Results
In HIV group there were 27% metabolic syndrome by IDF criteria and 26% by HOMA2-IR index (1.4 cut-off), 63% larger waist by IDF criteria and 26% abdominal obesity. To HIV/HCV coinfection group there were 30% metabolic syndrome by IDF, but 54% by HOMA2-IR index, 42% larger waist, but 52% abdominal obesity. To HCV group there were 25% metabolic syndrome by IDF and 38% by HOMA2-IR index, 67% larger waist, and 47% abdominal obesity.

Conclusions
The presence of HCV coinfection is responsible for alarming levels of insulin resistance, associated with a more favorable lipid profile that could act as a confounder in the clinical diagnosis of metabolic syndrome.

Disclosure
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EP648
Skin tags and metabolic phenotype in severely obese adults: the STAMP cohort study
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Introduction
Skin tags (acrochordons) are a recognised feature of insulin resistance, but the extent to which they predict an adverse metabolic profile or the response to lifestyle modification in severely obese adults is not known.

Aims
We sought to quantify prospectively differences in anthropometric and metabolic characteristics in severely obese adults with acrochordons vs those without acrochordons, and to determine whether the presence of acrochordons predicted how well bariatric patients respond to an 8-week structured lifestyle programme.

Methods
Weight, height, blood pressure, fasting glucose, and lipid profiles and a detailed dermatological assessment were conducted in a cohort of bariatric patients undergoing a structured lifestyle modification programme. Baseline differences between those with and without acrochordons were measured using a two-sample t-test, while differences in the response to the lifestyle intervention were quantified using linear regression.

Results
100 bariatric patients (mean age 50 ± 11.4 years, 31% males) were enrolled. There was a non-significant trend to those with acrochordons being heavier (weight 131.2 ± 26.6 kg vs 121.8 ± 15.3 kg, P=0.06) but also taller, with lower BMI (46.1 ± 7.8 kg/m² vs 47.3 ± 6.4 kg/m², P=0.53). They had higher HbA1c and systolic blood pressure (137.6 ± 15.5 mmHg vs 124.4 ± 9.1 mmHg, P<0.001), as expected. The intervention led to improvements in fitness and adiposity overall, but these improvements were no different in those with compared to those without acrochordons.

Discussion
In severely obese adults, acrochordons are an important marker of metabolic adversity but do not seem to predict the response to a lifestyle modification programme.

Disclosure
This project was funded by Diabetes Care West, the Diabetes Charity for the West of Ireland.

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Pituitary: basic and neuroendocrinology

EP650
Ectopic ACTH syndrome (EAS) is a rare cause of ACTH-dependent endogenous hypercortisolism.

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Introduction
Ectopic ACTH syndrome (EAS) is a rare cause of ACTH-dependent endogenous hypercortisolism.

Objective
The objective of this study was to analyse the clinical, biochemical, and radiological features, management, and treatment outcome of patients with EAS.
Design
It was a retrospective case-record study of 52 patients with EAS.

Materials and methods
Clinical, biochemical, and radiological features and response to therapy and survival were measured.

Results
The median follow-up was 7 years (range, 1–13 years). None of the dynamic tests achieved 100% accuracy. Imaging correctly identified the lesion at first investigation in 83% of cases. Bronchial carcinoid tumors were the most common cause of EAS (n = 34; 65.4%), followed by other neuroendocrine tumors (n = 13, 25%). In 9.6% (5) of patients, the source of EAS was never found. Octreotide scintigraphy and whole-body venous sampling were of limited value. Surgical attempt at curative resection was successful in 83% (43 of 52) of all patients; 9 (19.1%) responded generally well to bilateral adrenalectomy by vital necessity. Tumour histology and the presence of distant metastases were the main predictors of overall survival (P < 0.05).

Conclusions
No single test provides to find the source of EAS correctly. Despite a variety of tests and imaging studies for the correct diagnosis of the EAS, up to 10% of cases present an occult EAS. These cases require a prolonged follow-up, review, and repetition of diagnostic tests and scans, but, if it is necessary, do bilateral adrenalectomy.

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EP651
Assessment of GH-IGF1 axis in adults with beta-thalassemia major: when to do a GH stimulation test?
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GHD in adults (AGHD) is a clinical syndrome associated with lack of positive well-being, depressed mood, feelings of social isolation, decreased energy, alterations in body composition with reduced bone and muscle mass, diminished exercise performance, and cardiac capacity. These manifestations are also common in adults with beta-thalassemia major (BTM). Performing provocative testing in all patients is cumbersome and expensive. Many studies suggested that IGF1 may be used for primary screening, to avoid performing GH stimulation tests in the majority of healthy or diseased subjects, when appropriate normative sex and age-correlated ranges are available.

Objectives
The International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescence Medicine (ICET-A) promoted a study to collect more information on IGF1 values in young adult Italian BTM patients.

Methods
Plasma total IGF1 was measured by CLIA method for 120 patients with BTM (58M, 62F) with an age range of 26.0–53.2 years for females and 20.8–51.2 years for males. 64.4% of the patients were above 35 years of age. The mean BMI was 22.48 ± 3.34 kg/m².

Results
IGF1 data, expressed in percentiles. No significant differences were observed between IGF1 values in men and women with TM.

Analysis and discussion
On the basis of the present results and data from the literature, ICET-A concluded their survey with the following recommendations: a GH stimulation test should be indicated in presence of the following clinical and laboratory parameters: short stature (Height S.D. < −2.5), severe and/or prolonged iron overload, presence of severe osteoporosis and/or serum IGF1 level < −2 S.DS. In adult TM patients, with normal liver function, an IGF1 level < 50th percentile should be taken in consideration as a cut-off level for the GH assessment.

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EP652
IGF1 deficiency in newly diagnosed Graves' disease patients
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Introduction
Thyroid hormones influence GH/IGF1 axis, but previous studies reported discrepant results regarding serum IGF1 levels in hyperthyroidism. We have therefore investigated, at diagnosis, the relationship between serum IGF1 levels/IGF1 z scores and clinical and biological characteristics of Graves' disease (GD) patients. We also compared IGF1 levels/IGF1 z scores, at diagnosis, between GD and autonomous hyperthyroidism patients.

Methods
This cross-sectional study included 119 newly diagnosed hyperthyroid patients (98 with GD and 21 with toxic multinodular goitre) that presented consecutively to our clinic. The main measured parameters: TSH, FT3, FT4, TT4, thyroglobulin, TPOAb, ATA, TRAbs, and IGF1. Patients were considered IGF-deficient if IGF1 z score was ≤ −2 s.d. from mean for age.

Results
In GD patients men had higher IGF1 levels (P = 0.023) and IGF1 z scores (P = 0.013) than women. 18.4% of GD patients were, at diagnosis, IGF1 deficient. Compared with patients without IGF1 deficiency, these patients presented, at diagnosis, higher thyroglobulin (median = 72.55, IQR = 116.02 vs median = 11.40, IQR = 80.74 ng/ml, P = 0.002), FT (median = 11.30, IQR = 7.64 vs median = 7.33, IQR = 5.72 pg/ml, P = 0.027), and lower ATA (median = 20, IQR = 0 vs median = 34.05, IQR = 161 U/l, P = 0.001) levels. Thyroglobulin was identified as strong predictor for IGF1 deficiency (AUROC = 0.732, 95% CI: 0.620–0.844, P = 0.002) cut-off for thyroglobulin = 50.40 ng/ml. Se = 77.8%, Sp = 70%. IGF1 status was not influenced by gender (P = 0.08), current smoking (P = 0.55), goitre size (P = 0.53), ophthalmopathy (P = 0.33), TRAb (P = 0.23), and TPOAb status (P = 0.36). The prevalence of IGF1 deficiency was higher in GD patients compared to patients with toxic goitre (18% vs 0%, P = 0.033).

Conclusions
Our study shows, for the first time, the prevalence of IGF1 deficiency in nearly one-fifth of newly diagnosed GD patients. IGF1 deficiency was associated with lower ATA titre, higher thyroglobulin levels and more severe FT3 hyperthyroidism. The presence of active GO did not influence IGF1 status. GD patients had higher prevalence of IGF1 deficiency than patients with toxic multinodular goitre.

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EP653
The NAD- and NADP-dependent blood lymphocytes dehydrogenases level and their interaction with GH/IGF1 in active acromegaly
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Somatotropin (GH) and IGF1 realise their influence on the system of intracellular metabolism and a number of important biochemical lymphocytes reactions through the receptor apparatus. It is allows to use the peripheral blood lymphocytes as the investigations object of intracellular metabolism disorders in acromegaly.

Aim
To study the NAD- and NADP-dependent dehydrogenases activity in blood lymphocytes in active acromegaly patients.

Methods
The activity of NAD(P)-dependent dehydrogenases in blood lymphocytes was determined by biochemiluminescence method. The concentrations of GH and IGF1 were measured by ELISA.

Results
Studying the activity of mitochondrial NADP-dependent dehydrogenases found a decrease in all NAD-dependent oxidoreductase: NADIDH, NADGDH, and MDH (P < 0.01), which allows to state the low level flow in the tricarboxylic acid cycle. In active acromegaly were revealed the decreasing activity of all studied oxidoreductases: glucose-6-phosphate dehydrogenase (P < 0.01), NAD-lactate dehydrogenase (LDH) (P < 0.001), NADH-LDH (P < 0.001), NAD-malate dehydrogenase (MDH) (P < 0.001), NADH-MDH (P < 0.001), NADP-MDH (P < 0.001), NAD-glutamate dehydrogenases (GDH) and NADH-GDH (P < 0.001), NADP-GDH and NADPH-GDH (P < 0.001), NAD–isocitrate dehydrogenases (IDH) and NADP–IDH (P < 0.01 and P < 0.001 respectively), and glutathione reductase (P < 0.001). Our data observed that decreasing activity of NADP-GDH positively correlated with the basal GH level (r = 0.23,
P = 0.04) and NADP-MDH activity with IGF1 level (r = +0.30, P = 0.008). The low NADH-MDH activity negatively correlated to the basal GH concentration (P = -0.23, P = 0.04).

Conclusion
The chronic excess of GH and IGF1 in acromegaly causes a significant depletion of metabolic lymphocytes reserves. The main indicators of functional lymphocytes impairment in acromegaly are: the reduction of intermediates formation for the reactions of macromolecular synthesis and aerobic processes, the low concentration of glycolysis, nitrogen metabolism and inhibition of glutathione complex activity.

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EP654
Symptoms and complaints of patients with Cushing’s disease (CD) according to Moscow region database of patients with CD
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Objective
To evaluate the frequency of symptoms of Cushing’s disease (CD) at baseline and it dependence on different quantities.

Material and methods
Clinical and laboratory data of 44 patients with CD (40 females and four males, 37.9 ± 10.5 years old), duration of the disease 35.5 ± 22.75 months.

Results
Complaints: i) >80% – fatigability, weight gain, apathy, and headache, ii) 40–50% – loss of libido, brushtail, muscle weakness, insomnia, and hair loss, iii) <40% – irritability, sialia, back pain, memory loss, impaired wound healing, increased appetite, and acne. 6/15 (34.1%) patients with back pain had spinal fracture. One patient with spinal fracture had no back pain. Regular menstruation – in 5/40 (12.5%) women, 12 (30%) – menstrual irregularities, and 23 (57.5%) – amenorrhea. Clinical examination: arterial hypertension – in 100% (by BPFM). More than 70% had facial plethora, overweight/obesity, dorsocervical fat pad, hirsutism (females), and leg edema. BMI at baseline – 33.7 (30.4; 38.4).

Normal weight 7%, 16.3% – overweight, 76.7% – obese (34.9% – I grade).

Median weight gain 13.0 (10.0; 26.2) kg, correlated with duration of the disease (r²=0.35, P = 0.005; r²=0.3, P = 0.009; r²=0.2, P = 0.04; and r²=0.2, P = 0.049 respectively), ii) morning serum cortisol level with apathy and impaired wound healing (r²=0.1, P = 0.04 and r²=0.2, P = 0.006 respectively), iii) morning and midnight serum ACTH levels with increased appetite (r²=0.2, P = 0.01 and r²=0.3, P = 0.01 respectively), iv) midnight serum ACTH with fatigability (r²=0.2, P = 0.03), and v) UFC with supercaveicircular fat pads (r²=0.15, P = 0.04).

Back pain and sialia correlated with BMI (r²=0.1, P = 0.04 and r²=0.17, P = 0.006 respectively). Weight gain and acne had a positive correlation with duration of the disease (r²=0.2, P = 0.007 and r²=0.14, P = 0.001 respectively).

Conclusions
The most frequent symptoms of CD are nonspecific. The strongest correlation observed between symptoms and midnight serum cortisol and ACTH levels.

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EP655
Transgenic human gene reporter cell line for evaluating interactions between androgen receptor and xenobiotics
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Androgen receptor (AR, NR3C4) is a 110-kDa ligand-activated transcriptional factor that belongs to the steroid hormone receptor superfamily. It has broad importance. In our work, we describe construction and characterisation of a novel stably transfected human reporter cell line AIZ-AR for assessment of transcriptional activity of human androgen receptor. Cell line AIZ-AR is derived from human prostate carcinoma epithelial cell line 22Rv1 that was stably transfected with reporter plasmid containing three copies of androgen response regions (ARRs) followed by a single copy of androgen response element (ARE) from the promoter region of human prostate specific antigen (PSA) gene. Presented AIZ-AR cell line remained fully functional for over 60 days and more than 25 passages in the culture as well as after cryopreservation. Time-course analyses revealed that AIZ-AR cells allow detection of AR ligands as soon as after 8 h of the treatment. Upon dose–response analyses with 23 steroids in 96-well plate format, we observed induction of luciferase activity by androgens, but not by mineralocorticoids and oestrogens. Some glucocorticoids and progesterone also activated AR, but with potencies two to three orders of magnitude lower as compared with androgens. Taken together, we have developed a rapid, sensitive, selective, high-throughput and reproducible tool for detection of human AR ligands, with potential use in pharmacological and environmental applications.

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EP656
Diabetes insipidus as a rare neuroendocrine complication associated with Behcet’s syndrome
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Behcet’s disease (BD) is a chronic disease characterised by systemic involvement of blood vessels of all sizes on both arterial and venous circulation resulting in recurrent ulcers. The posterior infundibulo-hypophysis, causing DI, has been commonly reported in association with systemic inflammatory/autoimmune disorders, however there are a handful of cases presenting with DI and Behcet’s disease. A 26-year-old African-American woman diagnosed with BD in 2006 after receiving a flu vaccine resulting in oral and genital ulcerations. She presented to ED with malaise, dizziness, severe polyuria, polydipsia with requests for iced water. On physical examination there was evidence of multiple oral aphthous ulcers and genital ulcers. The serum level of sodium was 150 mEq/l, urine specific gravity was 1.003, and urine osmolality was 126 mOsm/kg. Estimated urine output volume was 5600 ml collected over 12 h. Complete evaluation of anterior pituitary hormone function tests including serum TSH, FT₃, FT₄, LSH, LCH, prolactin, IGF1, and ACTH stimulation test were unremarkable. MRI of the brain was suggestive of possible thickening of the pituitary stalk, but otherwise normal. Patient was started on oral DDAVP 0.1 mg twice daily with complete resolution of symptoms associated with DI. Formal water deprivation test was scheduled but not done due to a sudden resolution of DI over the course of 6 weeks.

Involvement of the CNS in Behcet’s can be severe, leading to a devastating neurological deficit. Central DI in patients with BD has been rarely reported with possible correlation to autoimmune mediated vasculitis involving the blood vessels supplying the hypothalamic. In contrast with all prior cases reported, our patient’s central DI had self-limiting course with complete resolution of symptoms (Molloy). Lymphocytic or autoimmune hypophysitis is commonly described as a transient but possibly relapsing condition.

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EP657
Effect of phenols and phthalates on rat and human pituitary cell proliferation
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**Methods**

Pituitary primary cultures were incubated with 250 pM–1.25 nM phenol or bis-(2-ethylhexyl)-phthalate for 24 and 96 h. Cell viability, apoptosis and proliferation were assessed by ATP lite (Perkin Elmer, USA), MTT assay (Sigma), Caspases 3–7 (Promega), and 5-bromo-2'-deoxyuridine labeling (BrDU-labeling; Roche).

**Results**

In rat pituitary primary cultures, ATP cell content was reduced by phenol (100 ± 2% vs 75.3 ± 3.4%, *P < 0.0001* control vs treatment) and bis-(2-ethylhexyl)-phthalate (100 ± 2% vs 83.2 ± 3.1%, *P < 0.0001*) at 24 h. After 96 h, ATP was clearly increased by phenol (100 ± 2% vs 123.9 ± 7%, *P < 0.05*, control vs treatment), less by bis-(2-ethylhexyl)-phthalate (100 ± 2% vs 111.4 ± 13%, NS). BrDU-labeling and MTT were also increased at the latter timepoint (BrDU-labeling: 100 ± 12% vs 136 ± 12%, *P < 0.05* and 100 ± 12% vs 137 ± 8%, *P < 0.05* for phenol and bis-(2-ethylhexyl)-phthalate respectively; MTT: 100 ± 4% vs 118 ± 5%, *P < 0.05* and 100 ± 4% vs 123 ± 10%, *P < 0.05*, for phenol and bis-(2-ethylhexyl)-phthalate respectively). No changes in caspase activation were observed at 24 or 96 h. In two human GH-secreting primary adenomas, ATP content was increased by 40 and 100%, respectively, after 24 h incubation with 650 pM phenol.

**Conclusions**

Our findings show than phenol and bis-(2-ethylhexyl)-phthalate initially reduce then increase pituitary cell energy content; further, long-term incubation with EDs is associated with increased cell proliferation. This study indicates that both normal and adenomatous pituitary cell proliferation is modulated by endocrine disruptors, thus supporting the role of pollutants in pituitary adenoma aetiology.

**Disclosure**

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**EP658**

Neuronal and synaptic ultra-structural organization in layer 5 of the human Gyrus temporalis

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Synapses are the key elements for signal transduction and plasticity in the brain. Despite a relatively large number of assumptions that have been made on the structure of mature cortical synapses in many other animal species, little is known about these structures in human. Hence, synapses in cortical layer 5 (L5), the main recipient layer of thalamocortical efferents, which representing the first station of cortical information processing were investigated structurally and quantitatively using serial ultrathin sections and digital electron microscopic images (DEM) followed by three dimensional (3D) reconstruction and immunohistochemistry against glutamine synthetase. The quantitative 3D-reconstructions of cortical synapses will allow to directly comparing structural and functional aspects of synaptic transmission and plasticity thus leading to a better understanding of the function of cortical networks in the human neocortex.

The structural parameters such as the size, number, and distribution of active zones as well as the size and organisation of the pools of synaptic vesicles were the most critical factors investigated not only for the induction but also for the maintenance of synaptic transmission and plasticity in the neocortex. The DEMI examination followed by 3D-reconstruction of cortical LS showed clearly a large pyramidal neurons (85%); GABAergic interneurons and astrocytes, multiple innervations on either the same or different dendrites, multivesicular bodies (MVBs) and mitochondria (two to eight) in the pre-synaptic element and perforations exist in the pre and post-synaptic densities. Besides, in 85% of the spines have a spine apparatus and a specialized form of endolysosomal reticulum.

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**EP659**

Influence of neurotransmitters on GnRH release in letrozole induced PCOS rat model

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Background

Polycystic ovarian syndrome (PCOS) is a common reproductive-endocrine disorder seen in women; characterized by increased GnRH pulsatility, hyperandrogenism, and cyst formation in ovary. GnRH release is controlled by higher centres of brain namely, hypothalamus and pituitary through various feedback mechanisms, one of them being neurotransmitters. However, no clear data is available with respect to GnRH regulation by neurotransmitters in PCOS. The aim of the present study was to evaluate status of neurotransmitters and their receptors in PCOS and to correlate this with GnRH pulsatility.

**Materials and methods**

PCOS was induced in rats using letrozole – an aromatase inhibitor – and validated structurally and metabolic characteristics of PCOS. Neurotransmitters were estimated from different regions of rat brain by HPLC and detected electrochemically. RNA was isolated from hypothalamus and pituitary of PCOS rats and used as template for reverse transcription. After synthesis of cDNA, CDNA expression was used for real-time expression studies of gonadotropins and neurotransmitter receptors. Transcripts were visualized using ethidium bromide and confirmed by sequencing. The data was statistically analyzed using GraphPad Prism 6.0 software.

**Results**

PCOS rats demonstrated increased hypothalamic GnRH1; pituitary GnHRH and LHβ mRNA levels as compared to control rats. Reduced levels of norepinephrine, dopamine, serotonin, γ-amino butyric acid, and epinephrine with increased glutamate levels were observed in pituitary and hypothalamus of PCOS rats as compared to control rats. Expression of neurotransmitter receptors – 5HT1A, GABA1, D2R, and z1A receptor decreased while that of NMDA receptor increased in hypothalamus and pituitary of PCOS rats.

**Conclusion**

Letrozole treated rat demonstrated hormonal and metabolic characteristics of PCOS with peripheral cysts in the ovary. Present study confirms that modulation in GnRH stimulatory as well as inhibitory neurotransmitters could have contributed to increased GnRH pulsatility, further resulting into increased LH to FSH ratio in PCOS.

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**EP660**

High metabolic risk is associated with small hypothalamic volume in acute lymphoblastic leukemia survivors 34 years after cranial radiotherapy

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Background

Metabolic complications (obesity, lipid abnormalities, and insulin resistance) are prevalent in acute lymphoblastic leukemia (ALL) survivors treated with cranial radiotherapy (CRT). The hypothalamus (HT) is a complex area involved in endocrine function and metabolic control. In ALL survivors, assessment of the volume of the HT in relation to metabolic parameters including ghrelin, a peptide stimulating food intake, has not been performed previously.

For the quantitative geometry study, the results showed a total pool of synaptic vesicles of 1671.57 ± 391.55 (ranging from 88 to 5841) with a mean diameter of 31.99 ± 0.87 nm, and a dense-core vesicles of 66.2 ± 11.72 nm, while, the volume of mitochondria and synaptic boutons and their surface were 0.05 ± 0.03 μm³, 0.63 ± 0.09 μm³, and 8.05 ± 0.27 μm² respectively. We can conclude that the morphological parameters observed in this study will help to better understand the mechanisms underlying synaptic transmission and plasticity in the adult cortical synapses.

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**EP662**

**Neuroendocrine complications of radiation therapy for pituitary somatotrophinomas**

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The purpose of the study

To examine the incidence of neuroendocrine complications after radiation therapy (RT) of pituitary somatotrophinomas.

Materials and methods

30 patients surveyed after receiving RT at a dose of 45 g in 25 fractions a day. Of these, 21 (70%) females, 9 (30%) men. The age of patients ranged from 36 to 71 years. 37% of them had pituitary macroadenoma with para-, supra-, and infrasellar growth. Duration of illness was 15 years on average. Period of observation after RT averaged to 10 years. The levels of GH, IGF1, PRL, TSH, LH, FSH, F4t, cortisol, oestradiol, testosterone, CT/MRI of the brain covering pituitary, visual field and acuity tests, and fundoscopy were assessed. All patients received RT in combination with drug therapy. 6 (20%) received RT with drug therapy, 11 (37%) after TAG and 13 (43%) were primary. All parameters were checked before (I group) and a year or more after RT (II group).

Results

The following impairments took place in I group: increased GH (M = 107), IGF1 (M = 1138) in 75%, and PRL in 33%; decreased gonadotropins in 80%, TSH and F4t in 17%, cortisol in 10%, decreased visual acuity in 30%, menstrual disorder in 62%, and impaired potency in 11% of patients. Group II showed following results: GH (M = 33) in 38%, PRL in 9%; decreased gonadotropins in 80%, TSH and F4t in 30%, cortisol in 50%, menstrual disorder in 67%, impaired potency in 33%, and decreased visual acuity in 57% of patients. Moreover, 20% developed ESS and 3% necrosis of brain tissue.

Conclusions

RT in pituitary somatotrophinomas leads to the stabilization of the pathological process.

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**EP663**

**Social stress promotes changes in local metabolism of glucocorticoids**

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Stressful experiences produce profound physiological and behavioural disturbances that may contribute to many psychiatric disorders. Stress activates HPA axis whose end products glucocorticoids modulate immune cells and cytokine activity. Local effect of glucocorticoids depends not only on its concentration but also on the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11HSD1), which amplifies intracellular glucocorticoid concentration by the conversion of inactive 11-dehydrocorticoesterone to active corticosterone. As cytokines are potent modulators of 11HSD1, it was interesting to establish whether cytokines could modulate metabolism of glucocorticoids in response to various stressors. Fisher 344 rats were exposed to chronic emotional homotypic stress (resident-intruder paradigm) or short-term variable stress combining emotional and physical stressors. Plasma level of corticosterone, TNFα and IL1β were measured by commercial kits, expression of 11HSD1, TNFα, and IL1β mRNAs by RT-PCR and 11-reductase activity by radiometric assay. We found that long-term homotypic stress increased corticosterone and decreased TNFα and IL1β in plasma. Expression of 11HSD1 mRNA was increased in thymus and spleen but not in mesenteric lymph nodes and liver. Similar pattern was found in expression of TNFα and IL1β – both cytokines were upregulated in thymus and spleen but not in liver and lymph nodes. Stimulatory effect of stress on 11-redutase activity was observed in both mobile cells and stroma of all three lymphoid organs. Vasotocin did not affect the stress-dependent upregulation of 11HSD1 in spleen and mesenteric lymph nodes. In contrast to chronic stress, the short-term variable stress up-regulated 11HSD1 only in thymus but not in spleen and lymph nodes.

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Disclosure
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EP664
The status of blood antioxidant system in patients with active acromegaly
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Introduction
The oxidative stress is supposed to be a key factor in multiple diseases. The aim of the study was to examine the effects of excessive GH secretion on the blood antioxidant system: total antioxidant capacity (TAC) of plasma; superoxide dismutase (SOD) and catalase activities (CAT); ceruloplasmin (CP); non-protein thiol (NT), and level of thiobarbituric acid reactive substances (TBARS).

Materials
Eleven patients with active acromegaly were included in the study. The state of the antioxidant system was examined and compared with those of a control group (nine persons).

Results
In patients with acromegaly the TAC levels and SOD activity were significantly lower (for 20 and 30%), than corresponding control data, whilst TBARS and CP levels were significantly higher (for 50 and 40% respectively).

Conclusions
The present work has demonstrated that parameters of the blood antioxidant system are impaired in patients with active acromegaly, what indicates the development of oxidative stress.

Disclosure
Authors have nothing to disclose.
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EP665
The PATRO adult study of Omnitrope® for the treatment of adult patients with GH deficiency: latest results
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Introduction
PATRO adults is an ongoing, international, open, longitudinal, non-interventional study of the long-term safety and efficacy of recombinant human GH (rGH; Omnitrope, Sandoz). The study will provide further data on the long-term safety of rGH in adult patients with severe GH deficiency (GHD). Here, we present safety data from an interim analysis.

Methods
Adults who are receiving treatment with Omnitrope and who have provided informed consent are eligible for inclusion. Patients treated with another rGH before starting Omnitrope therapy can also be included. The primary objective of the study is to assess the safety and efficacy of Omnitrope in adults treated in routine clinical practice. Particular emphasis is placed on the risk of glucose intolerance or diabetes and normalisation of IGF1 levels.

Disclosure
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EP666
Dose interval injection extension and costs of lanreotide Autogel 120 mg used in routine acromegaly care in Poland: 2 years data from Lanro study
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Objective
To determine the percentage of patients with acromegaly who received lanreotide Autogel 120 mg in extended duration interval and to evaluate the mean costs of ATG120 administered as part of routine care in Poland.

Methods
National, multicentre, non-interventional, observational prospective study with 2-years’ time horizon. The study population consisted of adult acromegaly patients who received at least three injections of ATG120 before inclusion. The endpoints were: percentage of patients treated with ATG120 at an extended duration interval (>4 weeks) and mean cost of ATG120. Costs were calculated in PLN from the public health-care payer and patient perspective for the year 2014 (one PLN = 0.25 EURO).

Results
151 patients suffering from acromegaly for at least 1 year were screened and 143 enrolled in 35 centres. Of those, 11 patients were excluded from the analysis because of missing of follow-up visits or because they did not complete the treatment period. 70% of them were women, 81% had macroadenoma, and 75% underwent surgical treatment in the past. During 2 years, changes in the treatment pattern decrease or increase of injection interval or change of treatment, were reported in 41 (31%) patients. In other patients treatment has not been changed. 63 patients (48%) received ATG120 at an extended duration interval. The mean number of days between injections was 35.1 (s.d. 8.2). ATG120 was predominantly administered in out-patient setting (84%) and by health-care professional (97%). The mean cost of ATG120 per patient per month was 402.5 PLN and 3.6 PLN from the public payer and patient perspective respectively. Meanwhile the retail price of ATG120 per pack is 4770.5 PLN.

Conclusion
The results demonstrated that extended duration interval of ATG120 is used in almost half of acromegaly patients, indicating the reduction of financial burden for the health care system.

Disclosure
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EP667

GH therapy has a beneficial effect on HbA1c levels in adult patients with GH deficiency: a report from the NordiNet® International Outcome Study

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Introduction
The clinical significance of the impact of GH on glucose homeostasis in adults with GH deficiency (GHD) remains unclear. We report the impact of 4 years of continuous GH therapy on HbA1c and progression to diabetes.

Methods
Data were analysed from patients with adult-onset GHD (>20 years old) enrolled in NordiNet® International Outcome Study (IOS) (NCT00960128), an observational study, and treated with GH (Norditropin®), Novo Nordisk A/S, Denmark for 4 years. Change in HbA1c (ΔHbA1c) from baseline was calculated for all patients, by GH dose group (<0.2 and >0.2 mg/day), for patients with clinically relevant decrease in HbA1c (≥0.3% decrease), unchanged, or clinically relevant increase in HbA1c (≥0.3% increase), and by baseline health status (% patients) (low-normal, HbA1c <5.8% (75.2%); pre-diabetes/high-normal, HbA1c 5.8–<6.5% (17.3%); diabetes, HbA1c ≥6.5% (7.5%).

Results
Among the 278 patients (48% females) mean±s.o. age was 49.4±14.5 years, BMI 29.0±6.1 kg/m² and HbA1c 5.29±0.85%. Patients receiving ≤0.2 mg/day GH (n=120) were older than those receiving >0.2 mg/day GH (53.9 years vs 46.0 years). At 4 years, 54.32% of patients had no change, 20.14% a decrease, and 25.54% an increase in HbA1c. ΔHbA1c at 4 years was greater for patients receiving ≤0.2 than >0.2 mg/day GH (0.10±0.61% vs −0.20±0.56%). A significant association (P=0.045) between GH dose >0.2 mg/day and the proportion of patients with clinically significant decrease in HbA1c (≥0.3% vs baseline) was observed. After 4 years, among patients with pre-diabetes/high-normal HbA1c at baseline (n=48), 48% had low-normal HbA1c, 10% developed diabetes, and 42% were unchanged. No overall association between change in health status (baseline to 4 years) and GH dose was found.

Conclusions
Four years of GH therapy was not associated with deterioration in HbA1c or progression to diabetes. Indeed, almost half of patients with pre-diabetes/high-normal HbA1c showed a clinically relevant improvement in health status after 4 years of GH therapy.

Disclosure
This study was sponsored by Novo Nordisk Health Care AG.

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EP668

Radio-induced meningioma: a long-term consequence of pituitary radiotherapy

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Long-term sequel of pituitary radiotherapy include hypopituitarism, optic nerve atrophy, sensorineural hearing loss, neurocognitive impairment and second intracranial neoplasms, the meningioma being the most frequent. The cumulative incidence of second cerebral tumours within 20 years of the radiation is 2% and, unlike its primary forms, they show a more aggressive atypical histology, and the age of appearance varies depending on the latency time, which in its turn is proportional to the dose of received radiation.

Material and methods
We present three patients with meningiomas secondary to pituitary adenoma radiation, all of them of somatomammotroph lineae. All these meningiomas were developed on the area of pituitary irradiation, over 20 years after it, and they were neither present on the diagnose nor was there an environmental or genetic predisposing condition.

Results
Case 1: A 65-year-old man, diagnosed with macroprolactinoma on 1977. He received cobalt therapy after a subtotal resection of the tumour. He debuted 29 years later with fronto-orbital cephalgia in relation with a prebullbar meningioma with extension to the foramen magnum.
Case 2: A 72-year-old male diagnosed with GH releasing macroadenoma in 1968. He was treated with cobalt-therapy and 44 years later presented with apathy and bradypisia. Neuroimaging revealed the presence of a right frontal convexity meningioma.
Case 3: A 50-year-old man, diagnosed with a macrolactinaoma on 1973 and treated with radiotherapy. After 40 years of treatment, a 1.1 cm meningioma is discovered on the right sylvian fissure following a study of dementia due to memory loss, mental dispersion, and depressed mood. The total dose of radiation received was 40–50 Gy on each patient.

Conclusions
Second cerebral neoplasms may appear more than 30 years after the pituitary radiotherapy and its detection advices permanent monitoring in neuroendocrinology consultations by means of periodic neuroimaging studies.

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EP669

MIR-7 has a role in behaviour of somatotroph adenopathen

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Purpose
IGF receptor 1 (IGF1R) and epidermal growth factor receptor (EGFR) are receptors tyrosine-kinase (RTK) whose altered signaling are critical factors in development of many types of tumours. These RTK are some of the main targets of the microRNA miR-7. This important tumour suppressor miRNA has the ability to inhibit the motility, invasiveness and anchorage-independent growth, suggesting a strong therapeutic potential in many types of cancer. Pituitary adenomas (PA) are a heterogenous group of tumors with diverse clinical behaviour. The aim of this study is to investigate the role of this miRNA in the behaviour of different PA subtypes.

Methods
In this cross-sectional descriptive study, we evaluated miR-7 by qRT-PCR on 60 human PA: 29 gonadotrophs (GT), 15 somatotrophs (ST), eight functioning corticotroph (CT), and eight silent corticotroph adenomas (SCA). Nine healthy pituitary from autopsies were used as calibrator reference. Aggressiveness was graded according to invasiveness (Hardy’s grade IV) and Ki-67 gene expression (>2.5-fold change (FC)).

Results
MiR-7 showed different expression depending on PA subtype (P=0.005). Its highest expression was found in ST (5.21 (2.06–5.80) FC), in which miR-7 was mainly overexpressed and only repressed in 33% of ST with high grade of aggressiveness. Thus, miR-7 repression entailed a risk of 7 (2–25) times higher to ST tumours reached high grade of aggressiveness (P=0.038). In addition, miR-7 was negatively correlated with age (r = −0.583, P = 0.022). In GT and SCA, expression was similar (0.91 (0.46–4.70) and 0.80 (0.26–3.18) FC respectively) and in CT, miR-7 showed its lower expression (0.69 (0.31–1.32) FC). However, we did not find associations with their behaviours.

Conclusions
According with our results, miR-7 plays an important role in the behaviour on SA, acting as tumor supressor mRNA and participating against its aggressiveness. Further studies are needed to clarify its potential therapeutic utility.

Disclosure
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EP670
The dynamics of anthropometric and hormonal parameters in adolescents (boys) with physical and sexual development during therapy with thyroid medications
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The purpose of research
To study the dynamics of anthropometric and hormonal indicators of adolescent boys with physical and sexual development (ZFPR) and iodine deficiency disorders (IDD), received treatment for 12 months replacement therapy of thyroid (jodormarin, t-thyroxine, Berlin-Chemie).

Material and methods
We have inspected and examined the whole for the period from 30th May 2012 to 15th October 2013 1066 adolescent boys in different regions of Uzbekistan. In the city of Bukhara and four districts of Bukhara region were examined 523 adolescents (boys) in Namangan region – 200, in Tashkent – 343, aged 11–17 years. The main contingent made up of college students and schools.

In the future, selected 163 patients with various disorders of growth and sexual development was carried spectrum of research includes the study of endocrine status, clinical, biochemical, and hormonal.

Among these patients, we have selected a further 60 adolescents with ZFPR (delayed puberty and growth)+ IDD from the city of Bukhara and Bukhara region, which were carried out additional studies (TSH, T4, X-ray hand, skull, EEG, Echo-EG, etc.) and anthropometric estimates the dynamics before and 12 months after replacement therapy with thyroid (jodormarin 100 and 150 mg/day, t-thyroxine 25 and 50 μg/day).

The results of the study
At 3, 6, and 12 months after treatment with thyroid dynamics in patients with mental retardation+ IDD there was a significant improvement in hormonal parameters, namely, the mean values of TSH and free T4 (P < 0.05). If the growth rate in patients with CP+IDD before treatment was 5.3 ± 0.2 cm/year, after 12 months of treatment with thyroid averaged 6.3 ± 0.3 cm/year (6.6–9.6 cm/year), and absolute increase growth in 12 months in average: 8.1 ± 0.4 cm.

Conclusions
Thus, on the basis of completed research can be concluded that therapy with thyroid in patients with mental retardation+IDD significantly improves both hormonal and anthropometric indicators, which confirms the need for primary prevention of IDD among children and adolescents.

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EP671
G protein signalling of native somatostatin receptors 2 and 5 in pituitary cells using a fluorescence-based membrane potential assay
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Somatostatin and dopamine receptors are the major G-coupled receptors in somatotrope cells that inhibit hormone secretion from the anterior pituitary. Prior to the anterior pituitary, we used a novel fluorescence-based screening assay to characterize somatostatin and dopamine receptor signaling in a time-resolved manner. This minimal-invasive technique provides a robust and reliable read out for ligand-induced receptor activation in permanent cell lines and primary pituitary culture. The pituitary cell line AtT-20 expresses both sst2 and sst5 endogenously. Exposure of WT AtT-20 cells to the sst2- and sst5-selective agonists BIM23120 and BIM23268, respectively, promoted a PTX- and tertiapin-Q-sensitive reduction in fluorescent signal intensity, which is indicative of activation of G protein-coupled inwardly rectifying potassium (GIRK) channels. In contrast, exposure to BIM23926 (sst1-selective), L-796/778 (sst3-selective), or L-803/067 (sst4-selective) did not produce any change in fluorescent signal intensity. However, after heterologous expression of sst1, sst3, or sst4 receptors BIM23926 and L-796/778 but not L-803/087 promoted a reduction in fluorescent signal indicating that sst1 and sst3 receptors can also couple to GIRK channels. Similar activation of GIRK channels by dopamine in AtT-20 required overexpression of D2 dopamine receptors.

Disclosure
German Research Foundation.

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EP672
The use of an oral salt load followed by furosemide in the treatment of euvolemic SIADH-induced hyponatremia
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Introduction
Furosemide can be used in the treatment of SIADH. However, to be effective, renal medulla osmolality (Osmmed) as reflected in urinary osmolality (Uosm) must be high. Sodium is the most important contributor to Osmmed, which increases following the administration of oral salt. We analyze the use of an oral salt load followed by furosemide for the acute/short-term treatment of euvolemic SIADH hyponatremia.

Methods
Retrospective analysis of nine patients with SIADH-induced hyponatremia and moderate hyponatremic encephalopathy receiving 4–5 g of oral salt, followed for 3 months later by 20 mg furosemide i.v. or 40 mg furosemide p.o (salt-plus-furosemide).

The results of the study
Basal: 4/9 (44.4%) were women. Median age: 69.3 (S.D.: 20.7). Prior to salt-plus-furosemide, SNa levels were descending in five out of six patients with a median change of −1.5 (IQR: −2.3 to −0.25), PNa: 121 (S.D.: 4.5). Initial SNa: 119 (s.d.: 4.8), SK: 4.4 (s.d.: 0.6), UNa 54 (IQR: 42.5–86), PNaSM 249 (S.d.: 7.9), and Uosm 252 (S.d.: 114). Following salt-plus-furosemide, SNa rose from 3 to 7 mmol/l, with a median increment of 5 (IQR: 4–7), reaching a SNa of 124 (IQR: 121–127), SK: 4.1 (S.D.: 0.4), UNa 66.4 (S.D.: 24.6), PNaSM 259 (S.D.: 7.4), and Uosm 370 (S.D.: 151.4). The SNa change post-salt-plus-furosemide vs the change prior to salt-plus-furosemide was statistically significant (P = 0.027). SK descent was also significant (P = 0.017). All blood pressure levels were below 130/85 mmHg before and after salt administration.

Conclusions
The oral administration of 4–5 g of salt followed by furosemide was useful for the acute/short-term treatment of euvolemic SIADH-hyponatremia in our patients. However, this therapy should not be attempted in severe hyponatremia, since a minimum 4 mmol/l SNa rise was not assured.

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EP673
Progressive reduction of tolvaptan doses in the treatment of chronic SIADH
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Introduction
Chronic tolvaptan (TV) therapy has been found to be safe and effective in the treatment of chronic SIADH. However, experience with modification of doses over time is limited.

Methods
We conducted a retrospective analysis of weekly TV doses (mg) in 41 patients with chronic SIADH treated for a minimum of 3 months, seen a week following discharge and monthly thereafter. Serum sodium (SNa) goal was 137–141 mmol/l, with 50% TV dose reduction when SNa fell between 130–131 mmol/l and 127–129 mmol/l, and 75% TV dose reduction when SNa fell below 127 mmol/l. If the growth rate in patients with CP+IDD before treatment was 5.3 ± 0.2 cm/year, after 12 months of treatment with thyroid averaged 6.3 ± 0.3 cm/year (6.6–9.6 cm/year), and absolute increase growth in 12 months in average: 8.1 ± 0.4 cm.

Conclusions
The oral administration of 4–5 g of salt followed by furosemide was useful for the acute/short-term treatment of euvolemic SIADH-hyponatremia in our patients. However, this therapy should not be attempted in severe hyponatremia, since a minimum 4 mmol/l SNa rise was not assured.

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Endocrine Abstracts (2015) Vol 37
Introduction
Cushing’s disease (CD) is responsible for 80% of endogenous Cushing’s syndrome (CS). However, distinguishing the cause of ACTH-dependent CS – CD vs ectopic CS – can be extremely difficult. Bilateral inferior petrosal sinus sampling (IPSS) has the highest diagnostic accuracy in this evaluation.

Objectives
The aims of this study were to determine the accuracy of bilateral IPSS in the differential diagnosis of ACTH-dependent CS and in predicting adrenocortical lateralisation in CD.

Design
We retrospectively analysed the ACTH levels in inferior petrosal sinus and peripheral blood samples of eleven consecutive patients with ACTH-dependent CS that performed bilateral IPSS between 2005 and 2014 in Santa Maria Hospital in Lisbon. ACTH levels from both inferior petrosal sinus and peripheral blood were measured before and after corticosteroid-releasing hormone (CRH) administration – 0, 5, 10, and 15’.

Ratios of central-to-peripheral and interpetrosal ACTH levels were calculated.

Results
IPSS was unequivocally performed in the eleven patients and it was suggestive of CD in nine patients, ectopic CS in one patient and inconclusive in another one. Concerning the nine patients with CD, the basal IPSS central-to-peripheral ratios were diagnostic for CD (> 2) in eight patients (88.9%) and the post-CRH IPSS central-to-peripheral ACTH ratios were diagnostic for CD (> 3) in nine patients (100%). ACTH lateralization was found (interpetrosal ratios ≥ 1.4) in eight patients (88.9%). In the patient with ectopic ACTH CS, the IPSS pre- and post-CRH ACTH ratios were negative, as expected. Transphenoidal surgery was performed in seven of the nine patients with CD and the histologic examination confirmed the diagnosis of ACTH-secreting pituitary adenoma in all of them. Two patients are waiting for surgery.

Conclusion
IPSS was a safe and well-tolerated procedure in our study group. It was effective in the differential diagnosis of ACTH-dependent CS and useful in planning CD surgical therapy.

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Introduction

In a majority of Spanish hospitals, serum sodium levels (SNa) are determined by indirect electrode methodology (sodium in the liquid fraction of serum) divided by the total serum volume (mmol/l). To avoid over/underestimating SNa, a formula can be applied: SNa corrected for total proteins (TP) = SNa × 93 divided by (99.1–0.7 × TP). Hypoproteinemia is frequent in patients receiving parenteral nutrition (PN), and is probably related to surgery, acute disease, and malnutrition. We have evaluated the impact of hypoproteinemia on the frequency and degree of hyponatremia in PN patients.

Methods

A retrospective study of patients prescribed PN from 01/11/11 to 01/06/12. SNa was determined at baseline and during PN, and corrected for TP. All sodium levels were corrected for glycemia and presented in mmol/l. Patients with triglycerides > 400 mg/dl were excluded. Indirect SNa (SNa) was compared to SNa as corrected for TP (TP-SNa). χ², Student’s, and Mann–Whitney U tests were performed. Results

222 patients were prescribed PN, 57.2% of whom were men. The median age was 75 (61–82). 47.3% were on the general surgery ward, 12% internal medicine, 12.1% oncology, and 8.6% hematology. 14.5% presented malnutrition (by BMI). Median duration of PN was 8 (5–14) days. Average baseline TP was 5.25 (S.D.: 0.76), with 93% presenting hypoproteinemia (TP < 6.5 g/dl). Baseline SNa: 138.1 (S.D.: 4.5) (P < 0.001), TP-SNa: 134.6 (S.D.: 4.5) with a difference of 3.5 mmol/l (95% CI: 3.4–3.6) (P < 0.001). 20% presented initial hyponatremia (SNa < 135 mmol/l) vs 52% (TP-SNa < 135) (P < 0.001). 28.7% developed SNa hyponatremia during PN, vs 64.2% with TP-SNa (P < 0.001), within 4 (2–7) and 3 (1–14) days respectively (P < 0.05).

Conclusions

Patients receiving parenteral nutrition often present hypoproteinemia. Therefore, correction of indirect SNa for total proteins becomes essential, both to avoid underestimation of the number of patients with hyponatremia, as well as to correctly take into account its degree.

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EP678

Long-term safety, tolerability, and efficacy of extended release somatostatin analogues

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Introduction

The main indications for the somatostatin analogues (SST-A) are acromegaly and/or neuroendocrine tumors. They can increase fecal fats, which could lead to the loss of fat soluble vitamins. There are few published studies showing the effects of the long-term use.

Methods

Retrospective study of patients with SST-A indicated from our endocrinology department in the last 10 years. We analysed indications and different epidemiological, clinical, and laboratory data, at baseline and after treatment with SST-A. Results expressed as: percentages (qualitative variables), average and s.d. (quantitative variables), with a significance level of P < 0.05.

Results

39 patients (66.6% women and 33.3% men) of 57.5 (13.68) years. Indications: acromegaly 71.8%, gastroenteropancreatic NETs 15.4% (four MEN1, one VHL, and one sporadic), gigantism 5.1%, advanced medullary thyroid cancer 2.6%, Graves’ ophthalmopathy 2.5% and thoracic neurofibroma in NFI 2.6%. 69.2% was treated with octreotide LAR average dose of 44.73 (32.27) mg/28 days and 25.6%, with lanreotide Autogel 46.5 (35.88) mg/28 days or both 5.1%. Durability of 57.12 (13.68) months. 7.6% were cured, 79.58% controlled the disease, 12.82% had persistent disease (two acromegalies and three NETs progressed). Side effects: gastrointestinal 17.9%, biliary 20.5% (7.6% asymptomatic cholecystitis, and 10.3% cholecystectomy), and 2.6% post-injection reactions. Analytical changes after treatment: HbAlc 6.3% (3.20) vs 6.5% (3.02), P = 0.008; AST 18.02 (6.97) vs 24.87 (25.78), P = 0.008; GGT 31.89 (44.09) vs 76.52 (160.75), P = 0.075, and FA 98 (68.92) vs 149.34 (202.74), P = 0.06. There were no significant differences in other analytical or vitamin parameters. 12.6% of patients discontinued treatment for: healing 7.6%, intolerance 2.5%, and ineffectiveness 2.5%.

Conclusions

SST-A are effective and well tolerated drugs. We found no evidence of malabsorption due to its use. Most frequent adverse effects were digestive, hepatobilary and glycemic alterations, as described in the literature.

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Endocrine Abstracts (2015) Vol 37
**EP680**

**Giant prolactinoma: a current challenge**

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**Introduction**

Giant prolactinomas are rare tumours, representing 2-3% of all prolactin (PRL)-secreting tumours. Their definition is restricted to pituitary adenomas with a diameter ≥ 2 or ≥ 4 cm of suprasellar extension, very high PRL concentrations (≥ 1000 ng/ml) and no concomitant GH or ACTH secretion. They are more common in young to middle-aged men. Endocrine symptoms are often present for a long period of time, but most times the diagnosis is made when neurological complications occur.

**Purpose**

We present a rare case of giant prolactinoma and review related literature.

**Clinical case**

The patient is a 40 years old male, with no personal or family history of endocrinopathy. On July 2014 he rushed to the Emergency Department at CHAlgarve due to a change in behaviour, confusion and loss of sphincter control occurring over the previous 2 days. The sellar-MRI showed a mass with 68×46×50 mm, intense contrast enhancement, involving intra and left parasellar with hydrocephalus and erosion of bone pavement. The patient underwent ventriculoperitoneal drainage and was admitted in the neurosurgery department. The laboratory study showed PRL > 2000 ng/ml (3.46-19.40 ng/ml) and free testosterone 3.1 pg/ml (7.20-23 pg/ml). He started cabergoline 0.5 mg/day, two pills per week. While recovering in the ward it was used as medical therapy which is reflected by expression somatostatin receptors in the adenoma.

To assess the sensitivity of granins – chromogranin A (CgA), secretogranin II (SgII), and secretoneurin (Sn) as biochemical and immunohistochemical markers of non-functioning pituitary adenomas (NFPAs): Methods

50 patients with NFPAs were included in the study. Tissue samples were immunostained for pituitary hormones, Ki-67, αSNU, CgA, SgII, and Sn. Furthermore, we have determined the levels of CgA, SgII and Sn in the plasma samples by ELISA method in patients before and after surgical treatment.

**Conclusions**

Of the 50 NFPA 27 (54%) were gonadotrophic tumours, 12 (24%) were null cell adenomas, immunopositivity for ACTH was determined in six cases (12%), for GH in four cases (8%), and for PRL in one case (2%). The median level of Ki-67 was 2.8% (min. 0.2% and max. 7%). We divided all patients in four groups by the degree of granin immunopositivity. High immunopositivity for CgA was found in ten cases (21%), for SgII in 17 (34%), for Sn in 24 (52%) compared to negative staining in 8 (17%), 10 (20%), and 2 (4%) respectively. High immunopositivity for all granin types was more frequent in gonadotropinomas, negative or slow staining for CgA and medium to high staining for SgII and Sn was more typical for ACTH and GH silent adenomas. The average serum CgA concentration before operation was 60.3 nmol/l (± 5.2), after surgical treatment 67.84 (± 9.8), SgII serum 24.9 (± 8.9) and 27.6 (± 8.9), plasma Sn 3.2 (± 0.2) and 3.4 (± 0.3) serum respectively. In healthy subjects the average levels of CgA and Sn were comparable with NFPAs patients 60.2 (± 10.5) and 4.1 (± 0.7), respectively, but healthy subjects had lower levels of Sn 14.8 (± 7.30). We did not found any correlation between granin levels and their tissue expression.

**Objective**

To assess the sensitivity of granins – chromogranin A (CgA), secretogranin II (SgII), and secretoneurin (Sn) as biochemical and immunohistochemical markers of non-functioning pituitary adenomas (NFPAs): Methods

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Of the 50 NFPA 27 (54%) were gonadotrophic tumours, 12 (24%) were null cell adenomas, immunopositivity for ACTH was determined in six cases (12%), for GH in four cases (8%), and for PRL in one case (2%). The median level of Ki-67 was 2.8% (min. 0.2% and max. 7%). We divided all patients in four groups by the degree of granin immunopositivity. High immunopositivity for CgA was found in ten cases (21%), for SgII in 17 (34%), for Sn in 24 (52%) compared to negative staining in 8 (17%), 10 (20%), and 2 (4%) respectively. High immunopositivity for all granin types was more frequent in gonadotropinomas, negative or slow staining for CgA and medium to high staining for SgII and Sn was more typical for ACTH and GH silent adenomas. The average serum CgA concentration before operation was 60.3 nmol/l (± 5.2), after surgical treatment 67.84 (± 9.8), SgII serum 24.9 (± 8.9) and 27.6 (± 8.9), plasma Sn 3.2 (± 0.2) and 3.4 (± 0.3) serum respectively. In healthy subjects the average levels of CgA and Sn were comparable with NFPAs patients 60.2 (± 10.5) and 4.1 (± 0.7), respectively, but healthy subjects had lower levels of Sn 14.8 (± 7.30). We did not found any correlation between granin levels and their tissue expression.

**Conclusions**

Our work shows that a majority of NFPAs are truly secreting adenomas with significant numbers comprising potentially hazardous corticotropinomas. CgA, SgII, and Sn have a high expression in most of the NFPAs, but their serum/plasma levels before and after surgical treatment were not much different from the controls and did not correlate with immunohistochemical results. So serum CgA and plasma Sn measurement do not represent a helpful biochemical marker of NFPAs potential hypersecretion, except of SgII, but this requires further study on a large sample of patients.

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**Endocrine Abstracts (2015) Vol 37**
**EP683**

The role of tolvaptan in syndrome of inappropriate antidiuretic hormone secretion: clinical outcomes and effect on length of stay

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Introduction

Hyponatraemia is the most common electrolyte imbalance among hospitalised patients. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is considered the most frequent etiology on patients with euvolemic hyponatraemia. Conventional treatment includes water restriction and salt tablets with limited efficacy and very slow onset of action in certain patients.

Material and methods

Systematic sampling of all SIADH patients treated with tolvaptan (group A, n=12) in our service over the last 2 years was compared to 12 within the conservative treatment group (group B). The average age was similar in both groups (A: 71.8 years vs B: 71.6 years) with a clear male predominance in the whole sample. The average plasma sodium was also similar (A: 123.4 mmol/l vs B: 123.8 mmol/l). SIADH etiology was mainly neurosurgical (A: nine patients and B: seven patients).

The length of hospital stays was compared with the time span until natremia normalisation in both groups. The statistical analysis used was Student's t-test. P value <0.05 was considered significant.

Results

The length of hospital stay from the beginning of the treatment was 11.1±8.1 days in the tolvaptan-treated group and 11.3±8.1 days in the tolvaptan-treated group (8.1 days in the tolvaptan-treated group and 16.7±2.7 days in the conservative-treated group (P=0.18). The mean hospital stay was higher for those treated with conservative therapy. Normalisation of natremia took 2.7±2.7 days in the tolvaptan-treated group and 11.3±9.4 days in the conservative treatment group. The speed of correction of the hyponatraemia was statistically significant for those in the tolvaptan-treated group (P=0.04).

Conclusion

Tolvaptan treatment in SIADH patients shows a rapid normalisation of natremia, effectively reducing inpatient length of stay.

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**EP684**

Opposite effects of dexamethasone and retinoic acid on neuronal actin cytoskeleton

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Brain ageing associates decreased neuronal plasticity, increased glucocorticoid and decreased retinoic acid (RA) signalling. We previously showed an interaction of these pathways on the regulation of a synaptic plasticity gene, BDNF. We thus investigated the effects of GC and RA on two BDNF-dependent genes: activity-regulated cytoskeleton protein (Arc) and Ca2+calmodulin-dependent protein kinase II (CaMK). Dexamethasone (Dex, 10^-8 M) and/or RA (10^-8 M) were applied on HT22 hippocampal cells during 4 days. Dex significantly decreased (55%) whereas RA increased cellular (145%) CaMKII mRNA compared to control. When combined RA decreased Dex effect. Dexam alone did not affect (95%) whereas RA increased (105%) Arc mRNA levels. When combined to Dex RA had the same effect on Arc mRNA as when used alone. As plasticity is closely related to the formation of cell processes, we investigated cell morphology and F-actin cytoskeleton organisation. Dexam affected cell morphology. Dexam-treated cells areas were significantly larger and rounder than controls and these increases were suppressed when RA was added. Actin expression (mRNA) and abundance (protein) were unchanged by Dexam. Conversely, phalloidin-stained polymerised actin was doubled by Dexam. RA suppressed this effect. Both cortical actin and stress fibres were significantly increased by Dexam (276% of control). RA suppressed this effect down to the level attained with RA alone: either moderately increased (100%) for cortical actin or decreased under control level for stress fibres (79%). Both glucocorticoids and RA target cell actin cytoskeleton and subsequently cell remodelling. The positive effects of RA on memory processes may then be due to counteracting some of the deleterious effects of glucocorticoids observed in brain ageing.

Disclosure

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**EP685**

The relationship of genetic factors to the development of nephrolithiasis in primary hyperparathyroidism

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Factors affecting the development of nephrolithiasis (NL) in primary hyperparathyroidism (PHPT) actively studied. CASR polymorphisms may be linked with the development of NL in PHPT. Supposed to the role of VDR in the development of nephrolithiasis in patients without PHPT. Objective

To assess the relationship of polymorphisms CASR and VDR with the development of the NL at PGPT.

Methods

The study included 187 patients with PTPT (54 (49; 64) years), 110 with NL and 77 without NL. The study of polymorphisms CASR (R909G, A986S, and Q1011E) in 166 patients (110 with NL and 56 without NL) were analyzed polymorphisms VDR – Apal, Bsml, Fokl, Cdx2, and Taql. The distribution of genotypes consistent with the condition of Hardy–Weinberg.

Results

The most common in both groups were polymorphisms R909G (23.6% vs 21.8%) and A986S (29.1% vs 37.9%) and Q1011E (16.4% vs 9.2%) met the most rare, the differences are not reliable (P>0.05). The genotype distribution was as follows CASR, with NL: AA-70.9%, AS-23.6%, SS-5.5%; RR-76.4%, RG-20.9%, GG-2.7%; QQ-83.6%, QE-14.5%, and GG-1.8%; without NL: AA-62.1%, AS-32.2%, SS-5.7%; QQ-90.8%, QE-8.0%, EE-1.1%, RR-78.2%, RG-19.5%, and GG-2.3%; not obtained differences in the frequency of genotypes and alleles CASR between the groups (P>0.05). VDR polymorphisms frequency did not differ between the groups (P>0.05), with NL: allele A-54.9%, a-45.1%; allele B-65.5%, b-34.5%; allele F-61.2%, f-38.8%; allele G 84.5%, A-15.5%; allele T-61.2%, and allele t-38.8%. In the group without NL: allele A-55.4%, a-45.5%; allele B-65.5%, b-59.6%; allele F-55.7%, f-44.3%; allele G-86.6%, A-13.4%; allele T-55.7%, and t-44.3%. The distribution of genotypes and alleles of VDR polymorphisms in the presence and absence of NL was not significantly different (P>0.05).

Conclusion

According to the results revealed a high prevalence of polymorphisms of VDR and CASR patients with PHPT. Development of NL is not associated with the presence of VDR polymorphisms and CASR.

Disclosure

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**EP686**

Pineal gland and thymus: structural and functional unity

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Neuroimmunoendocrine changes of the pineal and thymic function, are now believed to play an important role in the mechanisms of age-associated diseases development. Here we studied the morphofunctional and signal molecules unity of pineal gland and thymus during ageing. Autopsic pineal gland and thymus.
material sampled from people was divided into groups 1 – middle-aged people (60–74 years) and 2 – old people (75–89 years). Ultra-thin slices were used for electron microscopy. The study was carried out on the electron microscope JEM-100S. The identification of markers of signal molecules serotonin, melatonin, CD8, CD20 was carried out with immunohistochemical method using primary mouse MAbs, and secondary antibodies, biotinylated anti-mouse immunoglobulins. The data of electronic microscopy had shown the ultrastructure similarity of pinealocytes and thymic epithelial cells (TEC) in autopsy samples of pineal gland and thymus. Pinealocytes and TEC have the high number of round vesicles with, as we suppose, can consist biological activity signal molecules, in pinealocytes and TEC cytoplasm. These data can show that the both types of cells can belong to neuroimmunoendocrine system. By immunohistochemical method it was verified the expression of common signal molecules – endocrine cells markers (melatonin, serotonin) and lymphocytes (CD8, CD20) in the human pineal gland and thymus. The expression of melatonin, serotonin, CD8, CD20 in the pineal gland and thymus decreased during aging. Thus, the melatonin, serotonin CD8, CD20 expression in the pinealocytes and thymic cells confirms the unity of pineal gland and thymus as an neuroimmunoendocrine organs.

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EP687

Serum melatonin levels in pharyngo-laryngeal carcinomas
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Aim
To evaluate serum melatonin levels in patients with pharyngo-laryngeal malignant tumours preoperatively and after surgical excision of the malignancy.

Materials and methods
45 patients (41 men and four women, 59.7±4.2 years) and 35 age-matched healthy subjects have been tested for melatonin levels using ELISA method after serum extraction by reverse phase chromatography. Each patient had two blood samples, one in the morning and one at midnight in order to record the day and night melatonin levels. 19 patients (42.2%) presented a laryngeal squamous cell carcinoma, 22 patients (48.8%) pharyngeal, base of tongue or tonsil squamous cell carcinoma, and four patients (9%) had other malignant tumours in the head and neck region. Patients with β-adrenergic blockers medication have been excluded.

Results
43.7% of the patients had a T1 stage tumour, while T2, T3 and T4 stages were recorded in 18.75, 25.05 and 12.5% respectively. Biopsy revealed a squamous cell carcinoma in 82.9% of the patients. Tumour patients have been monitored postoperatively and their melatonin secretion tested after surgery as well (2 days after the surgery). Before surgery, cancer patients had significant lower levels of melatonin compared to healthy subjects. There were no significant changes immediately after surgical removal of the tumours.

Conclusion
Serum melatonin levels are lower in patients harbouring a pharyngeal or laryngeal tumour compared to healthy subjects. The idea of long-term recording of melatonin levels in head and neck cancer patients treated by different therapeutic approaches and future possibilities of using melatonin substitution in therapy is discussed.

Disclosure
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EP688

Plasma β-endorphins level is higher in lean patients with polycystic ovary syndrome than in lean women without this disorder
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Introduction
Polycystic ovary syndrome (PCOS) is one of the most common causes of anovulatry and infertility. According to the widespread data it affects 3–10% of women in the procreative age. Although many research have been done, it is still unclear which of mechanisms are responsible for the development of PCOS. The most up-to-date scientific trial indicates that the evolution of PCOS is related to the activity of the endogenous opioid system but precise mechanism is not completely understood.

Description of methods/design
26 lean women (BMI = 21.34 ± 1.83) were enrolled to the study and divided into two groups: group A consisted of 12 PCOS patients with FAI >5 and group B consisted of 14 women without features of PCOS and with FAI <5. Standard diagnostic hormone profile was made in all the patients and the level of β-endorphins was measured. The following hormones were measured: FT4, TSH, FT3, T4, T3, LH, estradiol, testosterone, cortisol, DHEAS, prolactin in metoclopramide test, insulin in OGTT, test, vitamin D3, C-peptide, CA125. BMI was assessed.

Results
Mean β-endorphin levels was significantly higher in group with FAI >5 (14.73 pg/ml ± 4.97 vs 7.26 pg/ml ± 2.62; Mann-Whitney test; P = 0.00018). Spearman test indicated also a positive correlation between β-endorphin level and weight (r = 0.682; P < 0.05) and β-endorphin level and C-peptide level (r = 0.778; P = 0.05) in FAI <5 group. Absence of the significant correlation was observed in FAI >5 group. It might be a consequence of limited number of this group.

Conclusion
Our study showed that the level of β-endorphins was statistically significant higher in patients with PCOS. Further experimental research is required to evaluate the correlation between β-endorphins and PCOS evolution.

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EP689

Gene panel study for familial pituitary adenoma
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Introduction
Several genetic syndromes are associated with familial pituitary adenomas. The penetrance of clinical manifestations of these syndromes is not ubiquitous and this might be the reason for the lack of detection of genetic mutations when only one or few genes are studied.

Aim
Clinical characterisation and molecular genetic study of a panel with ten genes involved in formation of pituitary adenomas in familial setting.

Materials and methods
Study included six families (13 patients) with familial pituitary adenomas with no other features of known genetic syndromes. Three families were with the homogeneous type of secretion (acromegaly) and three families with the heterogeneous type (acromegaly/nonactive pituitary adenoma). The study involved five men (38%) and eight women (62%).

Results
Mean age was 55.6 years (40–69 years), the average height for females was 160 cm, for males 170 cm. Most adenomas were GH-producing and non-secreting. The diagnosis of acromegaly was confirmed by hormone testing (GH > 2.5 nmol/l; no suppression on OGTT and high IGF1). Maximum GH was 23.9 ng/ml, medium — 13.9 (0.42–23.9). IGF1: maximum — 1817, medium — 1517 (439–1817). Minimum size of adenomas was 7 mm, maximum — 17 mm.
Tumour extensions were: supra – (three cases, 23%), latero – (two cases, 15%). In most patients, adenomas were extended in more than 2 directions. Genomic DNA from a blood samples of patients (probands) underwent high-throughput sequencing on an Ion Torrent Personal Genome Machine (Life Technologies) using a custom-designed AmpliSeq panel for the sequencing of a panel of genes (MEN1, CDKN1B, PKR1A, GNAS, AIP, SDHA, SDHB, SDHC, SDHD, PRKCA, CDKN2C, CDKN2A, POU1F1, PTTG2) but no pathological mutations were detected.

Conclusions

Families with hereditary pituitary adenomas can have tumours with homogenous and heterogeneous types of secretion. We were not able to show any genetic alteration in the group of patients studied.

Disclosure

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**EP690**

Quality of life in patients with acromegaly vs non-functioning pituitary adenomas and healthy control group

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**Objectives**

Acromegaly has an important impact on health-related quality of life. The aim of study was to ascertain the quality of life of patients with uncontrolled vs controlled acromegaly and compared to those with non-functioning adenomas and healthy control group.

**Methods**

124 participants underwent a cross-sectional assessment including the quality of life (AcroQoL, WHOQoL, BREF), psychiatric morbidity (GHQ-28) and acceptability of illness (AIS). The sample consists of patients with acromegaly divided into two subgroups accordingly to minimal GH concentration during the OGTT or profile of GH and level of IGF1; controlled and cured acromegaly group (CAG n=19) and active acromegaly group (AAG n=31); patients with non-functioning adenomas group (NAG n=37) and healthy control group (CG n=37) matched according to age.

**Results**

No significant differences were identified between CAG, AAG and NAG groups referring to quality of life, psychiatric morbidity and acceptance of illness. Compared with healthy controls, AAG group suffered more from anxiety and insomnia (P=0.031) and had significantly poorer quality of life in psychological domain measured with WHOQoL, BREF (P=0.004). In acromegaly group we observed statistically significant positive correlation between the level of IGF1 and prevalence of psychopathological symptoms measured by the GHQ-28. We also observed negative correlation with the level of GH and AcroQoL, in total score as well as in psychological dimension, including subscale ‘appearance’. The illness duration since diagnosis was identified as a negative predictor of physical dimension of AcroQoL (r=-0.35, P=0.035), social domain of WHOQoL (r=-0.43, P=0.009) and acceptance of the illness (r=-0.42, P=0.011).

**Conclusion**

Concerning the diagnosis, not only biochemical and radiological parameters, but also psychological aspect should be evaluated in acromegaly. IGF1 and GH could be an independent negative predictors of quality of life among those patients.

Disclosure:

Pbmn 118.

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**EP692**

Clinical experience in the treatment of acromegaly: 5 years follow-up results

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The aim of this study was to evaluate our clinical experience in the treatment of acromegaly during 5-year follow-up period.

**Methods**

Seventeen acromegaly patients (11 women and six men) monitored during 5-year follow-up period. A level of GH of <2.5 ng/ml and the normal IGF range were considered as the criterion for remission. The GH level and IGF1 level were evaluated every 6 months, while magnetic resonance imaging was taken every year during follow-up period.

**Results**

All patients had growth in hands and feet and typical facial asymmetry in the beginning of the study. Six patients had diabetes mellitus (35%), four patients had hyperprolactinaemia (24%), two patients had hypothyroidism (12%) and five patients had hypertension (29%). Visual field defect was in five patients (29%). Microadenomas found in six patients and macroadenomas in 11 patients. Nine patients were treated by trans-sphenoidal surgery. One of them was cured, three patients developed postoperative pituitary deficiency. Two patients were treated by transcranial surgery, but not cured. One of them was treated by Gamma Knife radiosurgery and after that developed pituitary deficiency. Sixteen out of 17 acromegaly patients were treated by octreotide (six of patients as primary therapy and ten patients as secondary therapy after surgery). Biochemical remission was achieved in 12 of 16 patients (75%) who received octreotide treatment. Tumour size decrease was achieved in 54% of patients. The treatment was successful withdrawn at five patient (29%) without recurrence for 2–3 years follow-up. One patient passed away due to co-morbidities and at one patient treatment was cancelled due to kidney cancer. Only one patient (6.25%) who regularly used high dosage of octreotide has uncontrolled acromegaly.

**Conclusion**

Our findings demonstrated that octreotide LAR treatment successfully controls clinical, biochemical and neuroradiological parameters.

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**EP691**

Acute octreotide suppression test in acromegaly: predictive value in long-term response to long-acting somatostatin analogues

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Introduction

The usefulness of acute octreotide suppression test (OST) in the selection of patients with acromegaly for chronic somatostatin analogues (SA) treatment is still controversial.

**Aim**

To investigate the predictive value of OST for long-term responsiveness to long-acting SA.

**Materials and methods**

Retrospective study of 25 drug-naive patients (13 males) with active acromegaly, subjected to an OST (hourly serum GH concentrations for 8 h were measured before and after last administration of s.c. octreotide 100 µg q8 h for 48 h). The mean achieved GH was used for analysis. GH nadir response during OST was also evaluated. GH<1 ng/ml and normal IGF1 (both evaluated as mean of three values) were used as parameters for biochemical control during SA therapy.

**Results**

On average, during OST a GH decline of 70.15±23.4% was observed in this cohort. Most patients (72%; n=18) showed a decrease > 50% of GH during OST (group A), while 28% had ≤50% GH reduction (group B). During SA treatment, 61.1% of group A achieved IGF1 and/or GH normalization, with a mean reduction of 54.6 and 68.2% respectively. In Group B, 28.5% reached IGF1 and/or GH normalization, with a mean reduction of 42 and 52.7%, respectively.

Biochemical control was observed in 11.1% of patients on group A and 14.3% on group B. In total, 36% of patients achieved a GH value <1 ng/ml during the OST. In this in 77.8% (n=7) had mean reduction >50% during OST. This test showed positive (PPV) and negative predictive (NPV) values of 64.71 and 71.43% for 50% GH reduction and PPV (66.67%) and NPV (56.25%) for minimal GH level <1 ng/ml during OST. A 50% reduction and a nadir GH<1 ng/ml during OST didn’t show correlation with the long-term normalisation of serum IGF1 and/or GH (P=0.106 and P=0.271 respectively).

**Conclusion**

In this cohort, a reduction of 50% and nadir GH<1 ng/ml following an OST weren’t predictive of remission on long-term SA as defined by updated criteria.

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A significant time- and dose-dependent decrease in cell proliferation was considered significant.

mRNA at 48 h showed a bimodal response, with a significant increase in gene GH.

Results
A significant time- and dose-dependent decrease in cell proliferation was observed in treated cells, with a simultaneous increase in GH concentration. GH increase was maximal at 48 h and reached about three-folds at 25 μM and four-folds at 50 μM (P<0.004 and P<0.0004 vs controls, respectively). Analysis of GH mRNA at 48 h showed a bimodal response, with a significant increase in gene transcription at 25 μM (P=0.0094) and levels similar to control cells at 50 μM (P=0.002 vs 25 μM). Compared to control cells, a modest increase in intracellular GH content was also observed at 25 μM, with a modest decrease at 50 μM, respectively.

Conclusion
Fenofibrate in its therapeutic concentration range is able to reduce cell proliferation which may reflect either an increased in GH synthesis (at low dose) or an increase in GH release (especially at high dose). It may be of interest to evaluate the clinical implications of these findings, especially in acromegals.

Disclosure
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EP695

Associations between radiological parameters and molecular phenotype in human GH-secreting pituitary tumours: could they help in predicting the appropriate medical therapy?

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Acronegaly is caused by excessive GH secretion from pituitary adenomas. Transphenoidal surgery is the first-choice treatment, but new drug therapies (e.g. somatostatin analogues, SSA) offer promising avenues for medical treatment. Complementary diagnostic tools may assist this strategy, helping to refine drug choice. Here, we investigate the associations between radiological features and molecular phenotype of pituitary tumours from acromegalic patients. This observational study included 17 acromegaly patients (38.4±15.6 years; 64.7% women), diagnosed from 2007 to 2012 at the Endocrinology and Nutrition Unit of the Reina Sofia Hospital, in whom surgery, radiology and molecular phenotyping of the adenoma was carried out. Magnetic resonance was performed to localise the tumours, which were all macroadenomas (94.0%) at diagnosis except for one microadenoma. Anterior–posterior mean diameter (APD) was 18.3±6.6 mm, inferior–posterior diameter (IPD) 18.8±6.7, and left–right diameter (LRD) 17.9±6.4 mm. Average volume was 33.36 mm³. Extracellular growth was observed in 73.3%, suprasellar growth in 60%, right sphenoid sinus invasion in 26.7%, left sinus invasion in 20%, and 20% in both sinuses. Compared to isointense adenomas, T2 hyperintense tumours showed greater IPD (23.4±5.3 vs 14.3±5.4 P=0.009), LRD (21.2±4.5 vs 14.6±7.2 P=0.035), total volume (45.2±2.6 vs 22±1.1 P=0.025), and Ki67 index (2.9±1.2 vs 1.1±0.5 P=0.036). T2 hyperintense adenomas had higher dopamine receptor subtype-5 (DR5) expression (P=0.038) and Ki67 (P=0.044). Adenoma IPD directly correlated with expression of DR5 (Rho +0.770 (P=0.006)) and somatostatin receptor subtype-3 (sst3) (Rho +0.549 (P=0.034)); and DR5 expression correlated with APD (Rho +0.735 (P=0.010)). Adenoma volume was directly associated with sst3 (Rho +0.535 (P=0.038)) and DR5 (Rho +0.736 (P=0.010)) expression. Ki67 index directly correlated with all diameters: APD (P<0.001), IPD (P<0.001), LRD (P=0.002); tumour volume (P=0.001); sst3 (P=0.015); and Ki67 (P=0.044). Our results reveal significant correlations among key pre-surgical radiological parameters and specific molecular phenotypic features of pharmacological relevance in GH-producing adenomas. Future studies should explore the molecular basis of these findings and their potential value in helping to select the appropriate medical therapy for these patients.

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Unravelling the role of stress regulators on GnRH release in Letrozole induced PCOS rat model

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Background and aim
Poly cystic ovarian syndrome is a multi aetiological female endocrinopathy wherein one of the major target organs affected is adrenal. It is important to note that adrenal plays key role in evoking stress mediated responses in brain; which can in turn affect GnRH, the main regulator of HPG axis. Along with corticotrophin releasing factor (CRF), newly discovered neuropeptides- urocortin2 and RF-amide related peptide-3 (RFRP-3) (mammalian GnIH analogue) are also known to modulate stress. However, complex regulation of GnRH axis via stress regulatory molecules and gonadal function adaptations is not clear. Thereby, current study was undertaken to elucidate the interaction of stress regulators with GnRH in PCOS pathology.

Material and methods
PCOS was induced in rat using letrozole-an aromatase inhibitor and confirmed for pathology. Hormones-gonadotropins, androgen, oestradiol, progesterone levels were measured by ELISA. Regulatory neurotransmitter-GABA was estimated by HPLC. Expression studies of GnRH regulatory neuropeptides and their receptors- CRF1, CRF1R1, Ucn2, CRF2R2, GnRH, GnRHR, RFRP-3, GPR-147 were carried out using real-time PCR.

Results
Hypothalamus and pituitary of PCOS rats demonstrated an increase in corticosterone (P<0.01) and androgen levels (P<0.01) whereas progesterone (P<0.05) and estradiol (P<0.01) levels were decreased. These altered levels of steroids were parallel to changes obtained in their receptors (GR, AR, ER-α, ER-β, PR). GABA levels were significantly decreased in hypothalamus (P<0.01) and pituitary (P<0.05) with reduced GABA1 receptor expression in PCOS rats. PCOS rats also showed significant alterations in mRNA expressions of Ucn2, RFRP-3 and GnRH1 with their receptors CRF2R2, GPR-147 and GnRHRR, respectively.

Conclusion
This study elucidates the complex regulation of GnRH in the hypothalamus and pituitary by stress elements- Ucn2, RFRP-3 and their involvement in altered GnRH release in PCOS pathology.

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Patients with neuroendocrine neoplasms: the experience of a referral centre in Greece

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Introduction
Neuroendocrine neoplasms (NEOs) are rare and heterogeneous neoplasms with variable biological behaviour but generally slow progression.

Methods/design
355 patients with NEOs registered in our data-base have been studied (166 females, mean age: 52 years; range: 11–88), during the period 2004–2014. TNM system has been used for staging and proliferation index Ki-67 for grading.

Results
Out of 355 patients, 35 (10%) had neuroendocrine tumours in the context of familiar disorders: MEN-1 (n=32) and Von Hippel Lindau (n=2). The following primary sites were registered: stomach: 56 (15.8%); duodenum: 13 (3.7%); pancreas: 131 (36.9%); small intestine: 40 (11.3%); appendix: 31(8.3%); colon: 14 (4%); lung: 27 (7.6%); thymus: 1 (0.3%); other sites: 22 (6.2%), unknown origin: 15 (4.2%); 4 (1.2%) had two concomitant neoplasms. 54 (15.3%) had functional syndrome. Metastatic deposits were found in 103 (29%) patients: bones: 16 (4.5%), lung: 5 (1.4%); liver: 94 (22.5%), peritoneum: 7 (2%), pancreatic: 2 (0.6%), brain: 2 (0.6%), omentum: 2 (0.6%), ovaries/kidneys/spleen: 1 (0.28%), 139 (47.8%) patients had Ki-67<2% (grade 1), 111 (31.3%) 3–20% (grade 2), 24 (8.2%) >20% (grade 3) for gastro-intestinal NEOs and for lung 4 (1.4%) atypical, 10 (3.4%) atypical, 1 (0.3%) large and 1 (0.3%) small cell lung carcinomas and 1 (0.3%) atypical thymic NEN. Stage1 were found in 135 (38.8%), stage2: 63 (18.1%), stage3: 48 (13.8%), staged: 102 (29.3%). 197 patients had surgical removal of the neoplasms, 46 had an endoscopic resection. The other systemic or local therapies that the patients received as monotherapy or in combination as first line treatment are as following: somatostatin analogs (n=100), chemotherapy (n=45), neoplasm-targeted molecular therapy (n=22), radio nucleotides (n=9), conventional radiotherapy (n=6), cauterisation with radiofrequencies/RFA (n=8), chemoresobilisation (n=6), interferon (n=2), 99 patients received second, 44 third, 23 forth, 12 fifth, 5 sixth line treatment. In the last follow-up of the present analysis 21 patients died from their disease: five had grade1 neoplasm, ten grade 2, two grade 3, one atypical thymic and another atypical lung NEN but two patients did not have an available Ki-67.

Conclusion
The present registry imply that the majority of the patients with NEOs have slow progression and long survival despite the presence of disseminated disease, confirming the necessity of the recent introduced therapeutic and diagnostic options following the guidelines as well as their management from referral centres under multidisciplinary teams.

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Review of assessment (diagnosis) of hyponatraemia
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Introduction
Hyponatraemia is the commonest electrolyte disorders encountered in hospitals. The aetiology of hyponatraemia is based on clinic assessment and biochemical investigations. However, studies have shown that recommended guidelines are usually not implemented.

Aim
Review of assessment (diagnosis) of Hyponatraemia and outcome based on length of stay (LOS) in hospitals.

Methods
A systematic search using PUB Med and Med Line, including an Internet search of published abstracts from British Endocrine Society, European Endocrine Society and Lung Oncology was conducted between 2002 and 2014 in UK hospital settings.

Results
18 publications were identified using search criteria using key word hyponatraemia combined with investigations, management and outcomes. Two were journal publications and the rest were abstract submissions which were of retrospective audit analysis of patients admitted with hyponatraemia in hospitals. Total of 2052 patients and the duration of the studies vary from 2 weeks to 52 weeks. There was wide variability with definition of hyponatraemia and S Na <130 and <125 mmol/l were commonly used. The aetiology diagnosis of SIADH was mentioned in all studies but only average score of 25% was recorded in all domains with regards to serum and urine osmolality and urine sodium. The average score improved to over 50% when cut off S Na was <125 mmol/l. The LOS was reported in nine studies and overall mean was 16 days.

Conclusion
Though the definition of hyponatraemia is <135 mmol/l, the audit findings seem to indicate there is higher threshold for detailed biochemical investigations when S Na is <125 mmol/l and to some extent when S Na falls to <130 mmol/l. This probably reflects under investigations with accurate diagnosis of hyponatraemia which would have an impact on management as shown in recent published study (Tzoulis et al., PGMJ 2014:01-5).

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Addisonian crisis as a manifestation of a partially empty sella in a 68-year-old woman
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Introduction
Empty sella syndrome (ESS) is a condition often discovered incidentally, where the sella turcica, the structure containing the pituitary gland, appears to be empty.
Patients either remain asymptomatic or, rarely, manifest signs of declined pituitary function. Patients experiencing hypopituitarism are offered hormonal replacement. Autopsy studies estimated a 5% EES prevalence among healthy individuals.

Case report
A 68-year-old post-menopausal woman, overweight (BMI = 29), mother of three children, presented with a 3-day history of fever (T = 38, 5°C), excessive vomiting and nausea and a history of 15 days of anorexia, weakness and fatigue. Five years ago, during the course of a hospitalization for the investigation of leukopenia, she was diagnosed with myelodysplastic syndrome. Physical examination yielded no pathological findings, whereas laboratory results revealed leukopenia (WBC = 2,900), hypokalaemia (K+ = 3.2 mmol/l), low TSH levels = 0.18 μIU/ml (n.v. 0.27–4.2), low FT4 = 6.01 pmol/l, (n.v. 12–22), decreased gonadotropin levels (FSH = 1.3 μIU/ml, n.v. in menopause > 30 and LH = 0.2 μIU/ml, n.v. in menopause > 10), hypocortisolaemia (cortisol = 51 nmol/l, n.v. 171–536 nmol/l) and normal ACTH = 17.3 pg/ml (n.v. 10–60). Adrenal function investigation with the short Synacthen test was positive (cortisol 0 min = 110 nmol/l, 30 min = 283 nmol/l, 60 min = 410 nmol/l) and MRI of the pituitary gland demonstrated a partially empty sella turcica, with herniation of the suprasellar cistern. The patient was diagnosed with panhypopituitarism and was initially treated with i.v. administration of methylprednisolone. After discharge, outpatient treatment included levotirothyroxine and prednisone.

Conclusions
Empty sella may be primary or secondary to surgery, irradiation or infarction of the pituitary gland. Idiopathic ESS usually generates from congenital defects of the sellar diaphragm where arachnoid membrane herniates through the deficient diaphragm, compressing the pituitary gland. In up to 50% of the cases, primary ESS is associated with benign intracranial hypertension. MRI usually demonstrates the compression of the pituitary tissue against the floor of the sella and the subsequent deviation of the pituitary stalk. Hypopituitarism is a rare complication of ESS as it manifests when >90% of the pituitary tissue is compressed or atrophied.

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EP700
Fracture of the left wrist as a possible indication of Cushing’s disease
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Introduction
Cushing’s syndrome is a rare (0.004%) hormonal disorder, which develops due to hypercortisolaemia. Cushing’s disease refers to a corticocorticol pituitary tumour overproducing ACTH, which induces abnormally increased cortisol production from the adrenal glands. Cushing’s disease is a causative factor of osteoporosis, hypertension, glucose intolerance and dyslipidaemia.

Case report
A 50-year old woman was referred to our department for the investigation of osteoporosis. She reported a 2-year history of weight gain, hypertension and hair loss and currently a fracture of her left wrist. Reported age of menopause, 49 years. On physical examination her blood pressure was 140/90, she was overweight (BMI = 25) and had bilateral supraclavicular fullness, buffalo hump, calf bruises and white striæ on the abdomen. Laboratory examination revealed shortened APTT, cosinopenia, increased fasting glucose, dyslipidaemia, high-normal sodium levels (Na+ = 145 mmol/l), mild hypokalaemia (K+ = 3.5), hypercortisolaemia (cortisol = 754 nmol/l, n.v. 171–536), FSH = 132 mIU/ml, LH = 36.9 mIU/ml, ACTH = 136 pg/ml (n.v. 0–60), PTH = 10.8 (n.v. 15.8–6.03) and 24-h urinary free cortisol = 436.4 μg/dl (n.v. 10–110). Estimation of lumbar spine bone mineral density by dual-energy X-ray absorptiometry was diagnostic of osteoporosis (T score = -3.3). The patient underwent dynamic investigation with dexamethasone-suppressed CRH stimulation (Δ-CRH) test, which indicated ACTH-dependent Cushing’s disease. 3 Tesla MRI of the pituitary gland suggested the presence of a microadenoma. Bilateral inferior petrosal sinus sampling (IPSIS) established the diagnosis of a microadenoma on the right anterior part of the pituitary gland. Treatment was started with pasireotide 2μg/d 2x/week.

Conclusion
Malnutrition in Cushing’s disease is by eight-times higher than in the general population, especially when the disease is not fully controlled. Unfortunately, many disease-related complications such as hypertension, dyslipidaemia and osteoporosis are not completely reversible when diagnosis is delayed. We suggest the diagnosis of Cushing’s disease to be considered in the differential diagnosis of osteoporotic fractures or osteoporosis.

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EP701
Clinical and molecular differences between invasive and non-invasive pituitary adenomas
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Pituitary adenomas are usually benign. However, a significant number of pituitary adenomas show an aggressive behaviour, with local invasion, increased risk of recurrence after surgery and lack of therapeutic response. In this study, we aimed to determine whether invasive and non-invasive pituitary adenomas display differences in clinical features and molecular parameters. In this retrospective descriptive study, 46 pituitary adenomas were analysed. Invasiveness was defined as invasion of surrounding structures like cavernous or sphenoidal sinuses on the basis of magnetic resonance imaging and surgical findings. Clinical variables, pathological subtype and need for radiotherapy were collected. Quantitative PCR was used to measure the expression of several membrane receptors important for pituitary function: somatostatin receptors (SSTR1–SSTR5), dopamine receptors (D1R-D5R) including the long isoform of dopamine D2 receptor 2, GHRHR, GHSRS1b, proliferation genes (ki67 and PTTG1) and housekeeping genes (HPRT, GAPDH and β-actin). 30 invasive pituitary adenomas (63.3% non-functioning; 23.3% GH-producing; 13.3% ACTH-producing) and 16 non-invasive adenomas (37.5% non-functioning; 43.8% GH-producing; 18.75% ACTH-producing) were analysed. No significant differences were observed in age and sex between invasive and non-invasive adenomas. Growth of tumour remnants (P < 0.001) and need for radiotherapy (P = 0.016) was higher in invasive adenomas. Only SSTR3 (P = 0.043), the long isoform of dopamine D2 receptor 2 (P = 0.048) and PTTG1 (P = 0.029) display significant differences between invasive and non-invasive adenomas. SSTR1 (P = 0.007), dopamine D2 receptor 2 (P = 0.019) and PTTG1 (P = 0.039) expression was higher in histological subtypes of aggressive pituitary adenomas. Our preliminary results indicate that invasive pituitary adenomas display differences in clinical features and gene expression. It remains to be determined whether these differences in gene expression might represent a mechanistic link to the invasion process.

Disclosure
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EP702
Molecular analysis of miRNA expression profiles in AIP mutation positive somatotropinomas
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Germline mutations in the aryl hydrocarbon receptor interacting protein gene (AIP) predispose to pituitary adenomas in young patients, often presenting as familial isolated pituitary adenoma (FIPA) kindreds. Pituitary adenomas in patients with AIP mutations (AIPmut) are usually somatotropinomas, which are more aggressive and have poorer responses to somatostatin analogues than their non-mutated counterparts. Given the rarity of this condition, the molecular pathogenesis of the AIP mutated tumors is still incomplete. The aim of this study was to determine the microRNA (miRNA) expression profile of AIP mutation-positive somatotropinomas. Tumours from patients carrying AIP mutations (AIPmut; seven tumors from six patients) were compared with somatotropinomas from mutation-negative individuals (AIPwt). RNA was extracted from formalin-fixed, paraffin-embedded tissues. For miRNA profiling, the GeneChip miRNA 1.0 arrays from Affymetrix were used. After filtering for

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EP703
Mortality in SIADH is similar to that in non-SIADH hyponatraemia; preliminary data

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Introduction
Excess mortality due to hyponatraemia is well documented but it is not clear whether the mortality associated with SIADH is different to that associated with non-SIADH hyponatraemia (NSH).

Methods/design
Prospective evaluation of all patients admitted with or developing hyponatraemia in a tertiary hospital (pNa < 130 mmol/l) in January 2015. Diagnosis of SIADH was based on standard clinical and biochemical criteria (pNa, spot urine sodium, urine osmolarity, O900 h cortisol and TFTs). Statistics were by Mann–Whitney U, Student’s t, or χ² tests, as appropriate.

Results (SIADH VS NSH)
180 patients were included. 89 (45 females) were classified as SIADH vs 91 (45 females) as NSH. Clinical data: mean age was similar; SIADH 68 years (s.d.: 15) vs NSH 72 years (s.d.: 15), P = 0.09. Premorbid history of hypertension, diabetes, COPD, liver disease, and cognitive impairment were similar (P > 0.05) but CCF (6.7% vs 30.7%, P < 0.0001) and ischemic heart disease (17.9% vs 31.8%, P = 0.02) were commoner in NSH. Laboratory data: admission pNa was similar; SIADH 126 mmol/l (s.d.: 5) vs NSH 126 mmol/l (s.d.: 3), P = 0.68. Other laboratory results (median, IQR). SIADH first: pC4: 4 mmol/l (3.6, 4.3) vs 4.1 mmol/l (3.7, 4.9), P = 0.003, pUrea: 5.3 mmol/l (4, 6.9) vs 11.6 mmol/l (7.4, 18.8), P < 0.0001, pCreatinine 64 mmol/l (53.5, 74) vs 128 mmol/l (85, 213), P < 0.0001, and spot uNa: 53.5 mmol/l (32, 89) vs 30 mmol/l (18, 59), P < 0.005.

In SIADH, O900 h cortisol: 482 mmol/l (IQR: 412, 578), 21% were receiving therapeutic glucocorticoids. One patient with COPD had a subnormal post Synachten peak cortisol of 363 mmol/l due to recent oral prednisolone course. No patient had hypothyroidism. Duration of hospital admission was similar: SIADH 13 days (11) vs 11 days (10), P = 0.55 and mortality was similar in SIADH, 5.6% compared to NSH 9.8% (P = 0.34).

Conclusion
Preliminary results show similar mortality rate in patients with SIADH compared to non-SIADH, although larger number of patients will confirm these observations.

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EP704
The higher gastrin levels were associated with better glycaemic control

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Background
Gastrin is an early incretin candidate, since it is released by oral glucose and potentiates the glucose-induced insulin secretion. It has been shown that only in hypoglycaemic or hyperglycaemic conditions gastrin release is influenced by changes in blood glucose and insulin concentrations.

Aim
To evaluate whether there is a relation between fasting serum glucose and serum gastrin concentrations.

Methods
Gastrin and glucose levels and HbA1c were measured in 202 blood samples. We studied gastrin serum concentrations dividing the samples in three subgroups with glucose concentrations <100, 101–126, >126 mg/dl, and in three subgroups with HbA1c <5.7, 5.7–6.4, >6.5%, and glucose levels in three subgroups with different gastrin levels 100–200, 200–500, and >500 ng/ml.

Results
Gastrin and HbA1c were negatively correlated (r = –0.27, P = 0.04) in the total population of samples studied. No difference was found in gastric concentration in the subgroups of normal, moderately increased, increased glucose concentrations (462.2 ± 311.9, 568.1 ± 164.9, and 387.8 ± 46.2 respectively), or in the subgroups of normal, prediabetic, diabetic range of HbA1c (520.8 ± 285.3, 428.7 ± 327.1, and 297.9 ± 236.5 respectively) but a trend value between normal and diabetic values (P = 0.08). In low, mid-high, high gastrin levels HbA1c (6.3 ± 9.7, 6.14 ± 0.7, and 5.8 ± 0.6) values but not glucose (109.2 ± 35.9, 111.6 ± 30.6, and 106.2 ± 25.4 respectively) levels different only between low and high gastrin levels (P > 0.001).

Conclusion
A negative correlation between glucose and gastrin levels has been shown in the present study. In patients with higher gastrin levels, HbA1c was statistically significant lower compared to patients with lower gastrin levels, indicating a better glycaemic control. Nevertheless further studies are needed to confirm these findings.

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EP705
Association of polymorphisms of VDR and CASR with clinical and laboratory manifestations of primary hyperparathyroidism

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Clinical manifestations and severity vary considerably primary hyperparathyroidism (PHPT) patients. Several studies indicate that the variation of clinical manifestations PHPT may be associated with genetic factors, in particular the VDR gene polymorphisms and CASR. The purpose of this study was to evaluate the effect of VDR gene polymorphisms and CASR on indicators calcium and phosphorus metabolism, levels of 25(OH)D, PTH, and condition of bone density in patients with PHPT.

Methods
The study involved 187 patients with PGPT (median age 54 (49; 64) years, 160/27/43). The study of polymorphisms CASR (R990G, A986S, and Q1011E). In 166 (139W/27M) patients analyzed polymorphisms VDR – ApaI, BstI, FokI, Cdx2, and Taq. The distribution of genotypes consistent with the condition of PHPT.

Paraclinical data: calcium, phosphorus in the blood, alkaline phosphatase, calcium in daily urine, CASR indicators calcium and phosphorus metabolism, PTH, 25(OH)D, and densitometry three parts of the skeleton. 25(OH)D was investigated during the period from November to May.

Result
17th European Congress of Endocrinology 2015

The analysis of polymorphisms of VDR revealed that polymorphisms FokI and BsmI influence the clinical manifestations PHPT. Carriers of FF genotype polymorphisms FokI level of 25(OH)D was significantly higher than that of genotype ff and Ff (P = 0.014). In carriers bb genotype polymorphism BsmI level of β-cross laps and osteocalcin was lower than the combined genotype Bb + bb (P = 0.036 and P = 0.041) and higher mean values of BMD in the spine (P = 0.038). Relationship with the calcium levels in the blood, urinary calcium or PTH has been received. There were no associations with different polymorphisms CASR indicators calcium and phosphorus metabolism, PTH, bone turnover markers, BMD in patients with PGPT.

Conclusion
The polymorphisms FokI and BsmI VDR may affect the clinic PGPT that is of interest, given the large variability manifestations PHPT. This result requires further study.

Disclosure
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EP706
Physiological area of normality of copeptin in normal-to-hyperosmolar states
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Background
Copeptin is the C-terminal portion of the precursor of vasopressin. In contrast to vasopressin copeptin is stable in vitro and easy to measure. Similar kinetics of both peptides have been described in different trials. However, the physiological area of normality of copeptin has never been evaluated.

Methods
We measured plasma copeptin, sodium, and osmolality levels in 93 healthy volunteers at baseline, during/after i.v. infusion of 3% saline until a sodium level of at least 150 mmol/l was reached, and during/after an oral waterload/v. infusion of glucose 5%. In total, 4–19 (median 12) measurements per patient were performed.

Results
Median age of the study participants was 28 years (range 20–54 years) with a balanced gender distribution male/female (46/47). Upon hypertonic saline infusion plasma sodium levels increased from a median of 140 mmol/l (s.d. 2.21) to 152 mmol/l (s.d. 2.44), plasma osmolality from 293 mOsmol/kg (s.d. 6.62) to 317 mOsmol/kg (s.d. 6.4) and plasma copeptin from 4.1 pmol/l (s.d. 4.56) to 34.2 pmol/l (s.d. 31.9). The maximal value of copeptin was reached after 150 min (s.d. 28.1), without a time lag to the maximum of plasma sodium or osmolality (reached after 145.39 (s.d. 150 (27.4) min respectively). There was a moderate to strong positive correlation between plasma copeptin and plasma sodium (r=0.58, P<0.05) and plasma copeptin and plasma osmolality (r=0.48, P<0.05).

Conclusion
There is a correlation between plasma copeptin, plasma sodium, and plasma osmolality levels from normo-to-hyperosmolar states.

Disclosure
SNF Prof. M Christ-Crain, Thermo Fisher Scientific.

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EP707
Pancreatic neuroendocrine tumour presenting with malignant hypercalcaemia
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Introduction
The aim of this report is to present the uncommon clinical presentation of a patient with a pancreatic NET.

Case report
A 55-year-old man with personal history of hypertension, dyslipidaemia, and depression. He was referred to the outpatient for high levels of calcium in repeated assessments during the last year. He referred polyuria and polydipsia. Initial biochemical assessment demonstrated: calcium 11.8 mg/dl, phosphate 4 mg/dl, creatinine 1.0 mg/dl, albumin 3.4 g/dl, sodium 135 mmol/l, potassium 4.3 mmol/l, and a normal TSH and T4. Ultrasound of neck revealed a hypoechoic lesion. Fine needle aspiration of lesion revealed a well-differentiated NET. The patient is clinically asymptomatic.

Conclusion
The manifestation of paraneoplastic syndrome due to PTHrP hypersecretion, despite its rareness in NET, should be considered in the differential diagnosis of hypercalcaemia in such tumours.

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EP708
The role of adipocytokine markers in the prognosis of survival and sepsis at critical postsurgical patients
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The secretion of adipocytokines is influenced by fat mass, but also by various situations related to acute stress (food deprivation, or critical state related to inflammatory or infectious syndromes). Adipocytokine secretory profile could be therefore used for the diagnosis of the type of critical state, as well for the evolution and survival prognosis of patients. The modifications of adipocytokine markers during the first hours after surgical intervention are insufficiently described. We characterised for the first time the precocious dynamics of leptin compared to classical inflammation markers (C-reactive protein and interleukin 6 (IL6)) during the systemic inflammatory response syndrome (SIRS) or sepsis at patients submitted to surgical intervention. Our prospective study included three groups of 20 patients: the SIRS group (SI) with major elective abdominal surgery, the sepsis group (SE) with community intraabdominal infections and the control group (C).

Leptin, C-reactive protein, an IL6 were measured at 0 point in all three groups and then serially for 5 days after surgery. We observed that leptin values increase precociously at 12–24 h in group SI (P<0.05), but remain within the normal range in the SE group. The patients from the SE group had a higher survival rate when they had higher leptin (>6 ng/ml) and lower IL6 levels (<150 pg/ml) within the first 24 h. The prognosis was worsened at patients having low leptin and increased IL6 at this time. Leptin has, therefore, a different precocious dynamics in SIRS than in sepsis patients. Early measurement of leptin levels, together with other inflammatory markers, may be useful for the differential diagnosis and prognosis of surgical critical patients.

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EP709
Triiodothyronine inhibits TSH secretion through a non-genomic mechanism
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TSH is the main regulator of the thyroid hormones (THs) synthesis/secretion, which in turn exert a negative feedback mechanism on the Tshb mRNA expression in the pituitary gland by reducing their transcription rate. Some of triiodothyronine (T3) effects are also shown in short period of time, characterizing the non genomic actions of THs. It has been shown previously that T3 acts on posttranscriptional steps of TSH synthesis and reduces its secretion when acutely administered to hypothryoid rats. The present study aimed to: i) characterize the pathways involved in the rapid inhibition of the TSH secretion induced by T3 in primary cultures of anterior pituitary cells and ii) evaluate the participation of T3 on calcium and magnesium intracellular mobilization in slices of pituitary of hypothryiod rats. The cultured plates were treated with three different stimuli, RGD (100 µg/ml – 50 min), Wortmannin (1 µM – 30 min), and EGTA (1 mM). Lately, T3 was added (10-9 M) for 30 min. Slices of pituitary were incubated with Fluor-4AM and Magnesium Green AM probes to address the mobilization of calcium and magnesium after T3 treatment. The results showed a rapid increase of TSH content in intracellular extracts while the amount of TSH in extracellular media was reduced after T3 challenge. The treatment with RGD and Wortmannin abolished T3 effects. No alteration on TSH secretion induced by T3 was observed in the presence of EGTA in the culture media neither in calcium intracellular...
mobilisation, while intracellular concentration of magnesium was altered under the same condition T3 treatment (16% of pituitary cells). The Therefore, we propose the existence of an additional mechanism that decreases the TSH synthesis/secretion, triggered in few minutes by T3, through its interaction with αVβ3 integrin at the plasma membrane, featuring a non genomic action of this thyroid hormone on its own synthesis/secretion.

Disclosure
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EP710

Patient reported outcomes comparing octreotide capsules to somatostatin analogues injections: results from a multicentre, baseline controlled, phase 3 study in acromegaly
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Background
Somatostatin analogues are the most widely used medical treatment in acromegaly. The available long-acting formulations are administered parenterally (i.m. or deep s.c. injections). Results of a multicentre, baseline controlled, phase 3 study have recently showed that octreotide capsules are an effective and safe treatment in acromegaly. The Treatment Satisfaction Questionnaire for Medication (TQ15M), assessed in the phase 3 study, as an exploratory endpoint, compared patient reported outcomes (PRO) in responders to injections vs. responders to oral treatment.

Methods
TQ15M, a validated PRO, consists of 14 multiple choice items encompassing four domains: effectiveness, side effects, convenience, and overall satisfaction. Additional supplemental items were developed specifically for this study and relate to wear-off effects/breakthrough symptoms and direct comparison of the overall satisfaction on octreotide capsules to injections. The results herein include a cohort of 88 patients (of 151 enrolled), who were controlled on oral and continued treatment with octreotide capsules up to 13 months.

Results
More patients reported improvement than deterioration in all domain scores for effectiveness, side effects, convenience, and overall satisfaction (improvement 41, 38, 48, and 39% respectively vs deterioration 28, 13, 39, and 29%, while others maintained their scores). The improved effectiveness score supported the improvement in acromegaly symptoms (AIS score), reported in the phase 3. Mean satisfaction with oral therapy compared to injections based on the direct comparative supplemental question – was 5.2 (scores 0–7), reflecting the answer ‘I am satisfied with this medication compared to others’ and aligned with 86% of core study completers electing voluntarily to continue into the extension phase.

Conclusions
Patients’ satisfaction with octreotide capsules was high. Improvements were noted compared to injections in all TQ15M domain scores, and specifically for effectiveness and side effects. These results correlate with patients electing to continue oral treatment and the improvements noted for acromegaly symptoms.

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EP711

Parenteral somatostatin analogues: a focus on injection site adverse reactions
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Introduction
Injectable somatostatin analogues (SRLs) are the standard medical management of acromegaly. Injection site adverse reactions reported for parenteral SRLs were examined in the literature and in the FDA Adverse Events Reporting System (AERS), and compared to the respective drug labels.

Methods
PubMed was searched using criteria: period 1995–2013, drugs – octreotide (Sandostatin®), lanreotide (Somatuline®), or somatostatin analogues and adverse reactions of interest – e.g. injection site reactions, in treatment of acromegaly and/or cancerous tumours. FDA AERS files were reviewed for period Q1/2004 to Q1/2014. Adverse events reported in patients treated with somatostatin analogs were extracted as follows: i) drugs – octreotide (Sandostatin®) and lanreotide (Somatuline®), ii) adverse events on which somatostatin analogs were the primary or secondary suspected drug, and iii) preferred terms (MedDRA) containing the keywords: Injection site, Application site and Administration site.

Results
Literature data showed injection site pain in up to 76%, with severe pain in 11%. Other adverse reactions included injection site erythema, hematoma, bruising, edema, induration, nodule formation, pruritus, and lipoedema. In AERS the most frequent injection site adverse reactions reported were injection site mass (85 cases), haemorrhage (74), swelling (41), induration (29), discomfort, erythema, nodule (28 each), and haematoma (26). AERS cases increased annually from ten in 2004 to 434 in 2012 with a total of 858 AEs by case and 2389 AEs by individual report by Q1/2014.

Conclusion
The incidence of injection site adverse reactions in both the literature and the FDA AERS database is higher than that reported in respective somatostatin analog labels and includes AEs of significant concern. Because of the nature of reported injection site AEs and their potential physical burden to patients, an oral alternative to chronic parenteral injections would mitigate these parental adverse events and significantly benefit patient care.

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Pituitary: clinical

EP712

Sheehan’s syndrome: a clinical, biochemical, hormonal, radiological, bone mineral density, and quality of life assessment
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Background
Sheehan’s syndrome or postpartum pituitary necrosis though rare, is still remains one of the commonest causes of hypopituitarism in the developing parts of world like Indian subcontinent. The clinical presentation is often variable and frequently accompanied by hypogonadism which leads to low bone density due to loss of bone protective effect of oestrogen.

Aims
To find out the bone mineral density and the quality of life (QoL) in patients of Sheehan’s syndrome, and to find out the effect of hormonal replacement therapy on outcome.

Material and methods
All patients previously diagnosed as Sheehan’s syndrome or newly admitted during the study period of 3 years were enrolled in the study after obtaining an informed consent. Their clinical, biochemical, hormonal, radiological, and bone mineral density (BMD) data were collected. QoL was assessed using the disease-specific QoL, both before and after hormone replacement therapy.

Results
Twenty-three patients were enrolled in the study, the mean age of diagnosis was 43.4±14.2 years; mean diagnostic delay was 13.2±7.4 years. Secondary amenorrhea and lactation failure were the most common clinical presentations. The bone mineral characteristic of patients with Sheehan’s syndrome, reveals T-score, were found to be significantly reduced in lumbar spine (~−2.8±0.6) and femoral neck (~−2.9±0.8) as also Z-score; these are ~−1.6±0.6 and ~−1.4±0.6 respectively. Severe osteoporosis (osteoporosis with fracture) was found in three patients (13%), osteoporosis in four patients (17.3%), osteopenia in six patients (26%), and rest ten patients had normal BMD. The QoL of patients with Sheehan’s syndrome before and after hormonal replacement therapy for 1 year, before start of therapy the score was 25±8 and it increased to 59.4±8.6 after 1 year of hormonal replacement therapy.

Conclusion
Sheehan’s syndrome resulted in multiple pituitary hormone deficiencies in all the patients. Low bone mass and low QoL were frequently seen in patients with Sheehan’s syndrome. Both low mineral density (P<0.05) and QoL improved significantly (P<0.05) after hormonal replacement therapy.

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A 17-year-old girl was referred to Endocrinology Unit by her neurosurgeon. She had complained of severe headache, palpation induced galactorrhea on left mammary and visual abnormalities for 1–2 months. Her menstrual period was regular. On physical examination a pale face and fatigued appearance was noticed. Biochemical and hormonal analyses are as follows: fasting glucose level was 84 mg/dl, serum sodium level was 140 mEq/l (135–145), serum potassium level was 3.9 mmol/l, FSH level was 9.24 mIU/ml, LH level was 13.26 mIU/ml, oestradiol level was 70 pg/ml, prolactin level was 22.14 ng/dl, cortisol level was 16.13 µg/dl, free T4 level was 0.9 µg/dl, and TSH level was 2.01 mIU/ml. Her urine analysis showed a normal density. The laboratory analyses did not reveal any anterior or posterior pituitary deficiencies or excess. She underwent a pelvic and breast evaluation for palpation induced galactorrhea which has existed the last 6 months. Her pelvic ultrasonography revealed a 2.5 cm hypechoic mass on her right paraaerian area. Magnetic resonance (MR) examination showed a 3.5 × 4 cm right adrenal mass. Signal characteristic of mass was suggestive of dermoid cyst. Breast ultrasound revealed a 18 × 11 mm hypechoic heterogeneous solid lesion. Histopathologc examination of the breast mass was consistent with fibroade- noma. Pituitary MR revealed a 10.8 × 6.5 × 7 mm sellar mass with homogenous hyperintensity on T1 weight imaging. The mass was localised posteriorly on left pituitary gland. The features of mass was considered to intense cystic adenom or rathke cleft cyst. The coexistance of pituitary cyst, dermoid ovary cyst, and fibrocystic mammary adenoma was seen in the presented case. Patients with cystic lesion in any tissue should be screened for cystic lesions in other compartments of the body and those cystic lesions including solid components should be followed for the functional activation or loss and malign transforman.

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Conclusion
Mild hyperglycaemia at the start of pasireotide is not the reason for discontinuation. According to our best knowledge this is the first case reported of sudden lack of efficacy of pasireotide after long-term effective treatment.

Disclosure
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**EP717**

**Isolated pituitary sarcoidosis stained with a specific MAB against Propionibacterium acnes: a case report**

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Introduction
Sarcoidosis is a systemic granulomatous disorder usually affects multiple organs. Approximately 10% of sarcoidosis occurs as isolated neurosarcoidosis in CNS and < 10% of neurosarcoidosis develops in a restricted hypothalamic–pituitary area. Recent study has identified Propionibacterium acnes in lungs and lymph nodes of many patients with sarcoidosis using a MAB specific for this bacterium (PAB), providing strong evidence for P. acnes as a pathogen of sarcoidosis (Modern Pathology, 2012). We report a case of isolated pituitary sarcoidosis, manifested as an acute onset of secondary adrenocortical insufficiency.

Case
A 29-year-old man suddenly developed severe headache, malaise, and appetite loss 1 year after an extensive skin peeling therapy for pimples. MRI revealed a diffusely and symmetrically enlarged pituitary, protruded upward with a thickened stalk and inhomogeneously enhanced with gadolinium, suggesting anterior hypophysitis. Endocrinologically, baseline ACTH and cortisol was 4.8 µg/dl and 0.4 µg/dl respectively. FT₄ was 0.72 ng/dl, testosterone was 10.3 ng/dl, PRL was 36.1 µg/l, and peak GH response to GHRP2 was 2.3 µg/l. Administration of hydrocortisone improved clinical symptoms and recovered hypogonadism and hypothyroidism by 2 weeks. Blood levels of ACE, lysozyme, and IgG4 were normal. Whole body gallium scanning did not detect any organ involvement other than the pituitary. Pituitary biopsy revealed many non-caseous granulomas accompanied with calcification. Immunostaining with PAB was positive for giant cells and infiltrated mononuclear cells. This patient fulfilled a diagnostic criterion of neurosarcoidosis by clinical manifestation of hypopituitarism, exclusion of other systemic inflammatory disorders, and histological identification of typical sarcoid granulomas.

Conclusion
Isolated pituitary sarcoidosis is an extremely rare inflammatory disorder. Currently six cases were reported and only three of them were biopsy-proven. This is the seventh case of isolated pituitary sarcoidosis and the first case in which P. acnes were identified definitely in sarcoid granulomas of the pituitary.

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**EP719**

**Somatostatin analogues effectiveness in non-functioning pituitary adenomas in comparison with acromegaly**

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Introduction
Somatostatin analogues (SSAs) are used in the treatment of somatotropinomas. Actually, the use of these drugs in clinically non-functioning pituitary adenomas (NFPA) is raised. The aim of the study is to assess the effectiveness of SSA therapy in both groups.

Materials and methods
40 acromegalic patients and 22 patients with NFPA were treated with SSA for the total therapy duration up to 10 years. Hormonal profile, dynamics of tumour size changes, ophthalmic exam with assessment of visual field, somatostatin receptor scintigraphy, immunohistochemistry of somatostatin receptor subtypes of operated tumours as well as patients’ quality of life and undesirable effects were analysed.

Results
The significant decrease of GH and IGF1 concentrations was noticed in 95% of acromegalic patients (16 recurrent tumours and 24 primary tumours). The complete normalisation of hormone levels was observed in 57.5% of patients. The evaluation of the tumours’ size in MRI revealed their significant decrease in 40% of acromegalic patients including 81% of primary adenomas. The quality of life was improved in almost all patients. Two patients developed cholelithiasis with indication to cholecystectomy. Considering the patients with NFPA the stabilisation of tumour size and visual field was observed in 68% while the reduction of tumour size was noticed in 9% of cases. 23% of patients revealed an increase of adenoma size regarding the reoperation.

Conclusions
SSAs are effective in the treatment of acromegaly. In patients with NFPA the effectiveness of SSA is much lower. However, pharmacotherapy with SSA in the cases of NFPA allows the stabilisation of the disease and can be considered as an alternative for the next neurosurgeries.

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**EP720**

No evidence of impaired oral hormone substitution after gastric bypass surgery in patients with morbid hypothalamic obesity and hypopituitarism secondary to craniopharyngioma

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Background

Craniopharyngiomas (CP) are benign brain tumours presenting in childhood treated by tumour resection together with radiotherapy. In about half of the cured patients hypothalamic damage leading to eating disorders and obesity as well as to hypopituitarism, necessitating consequent hormone substitution therapy, is observed. Bariatric surgery is an efficient treatment strategy for morbid obesity. However, so far it is unknown, whether oral hormone substitution is hampered by impaired intestinal absorption, leading to severe hypopituitarism or adrenal insufficiency.

Methods

Four CP patients with hypopituitarism and morbid obesity treated by gastric bypass surgery were included in this retrospective analysis. Dosage of hormone substitution, hormonal blood concentrations, adverse effects of impaired drug absorption, and anthropometric characteristics were investigated pre and 3–12 months post operatively.

Results

In all CP patients (3W/1M; BMI_{basal} 49±7 kg/m²) gastric bypass resulted in distinct weight loss (~35±27 kg). In follow-up examinations mean concentration of T\_4 increased (T\_4_{basal} 0.9±0.31 ng/dl vs T\_4_{follow up} 1.28±0.29 ng/dl). No patient developed any signs of adrenal insufficiency postoperatively. Mean daily dosage of oral thyroid hormone substitution (levothyroxine basal 156±244 μg/day vs levothyroxine_{follow up} 150±10 μg/day) and hydrocortisone (hydrocortisone_{basal} 29±12 mg/day vs hydrocortisone_{follow up} 26±2 mg/day) was unchanged. Mean IGF1 concentration decreased after weight loss (IGF1_{basal} 217±93 ng/ml vs IGF1_{follow up} 111±56 ng/ml), whereas daily growth-hormone substitution was slightly increased (somatropin_{basal} 0.9±0.5 mg/day vs somatropin_{follow up} 1.0±0.4 mg/day). Minirin dosage and daily fluid intake remained unchanged.

Discussion

Our results in n = 4 CP patients suffering from hypopituitarism indicate that oral hormone substitution therapy is not impaired following gastric bypass operation, probably making it a safe and considerable treatment strategy in patients suffering from hypothalamic obesity.

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**EP721**

Cabergoline is an effective treatment for clinically non-functioning pituitary adenomas

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As optimal postoperative management of patients with clinically nonfunctioning pituitary adenomas (NFPAs) is a matter of debate, the role of dopamine agonist (DA) therapy in this clinical setting was evaluated.

Methods

Retrospective analysis of prospectively collected data was conducted at two pituitary referral center with different standard practices for post-operative management of NFPAs: DA therapy or conservative follow up. Dopamine receptor 2 (D2R) expression was examined by immunohistochemistry. D2R long and short isoform mRNA expression was measured by quantitative RT-PCR.

Results

Seventy-nine patients (mean follow-up, 8.8±6.5 years) were treated with DA, either initiated upon detection of residual tumour on postoperative MRI (preventive treatment (PT) group, n=55), or when tumour growth was detected during follow-up (remedial treatments (RT) group, n=24). The control group received no medication and comprised 60 patients (mean follow-up 6.3±2.5 years). Tumour mass decreased, remained stable or enlarged respectively in 38.2, 49.1, and 12.7% of patients in the PT group. Shrinkage or stabilization was achieved in 58.4% of the enlarging tumours in the RT group, whereas tumour growth persisted in only 41.6% of them. In contrast, tumour size enlarged in 53.3% and remained stable in 46.7% of subjects in the control group (P<0.0001 for all comparisons). 15 years progression-free survival rate was 0.805 for the PT group, 0.48 for the RT group and 0.12 for controls; P<0.0001 (PT vs control), P=0.04 (RT vs control), and P=0.0053 (PT vs RT). 41.7% of patients in the control group required additional surgery or radiotherapy as compared to 20.2% of the combined treatment groups (P=0.00084). There was no correlation between D2R expression and tumour response to DA treatment.

Conclusions

Dopamine agonist therapy is associated with decreased prevalence of residual tumour enlargement in patients with non-functioning pituitary adenomas, particularly when treatment is instituted prophylactically after surgical resection. Disclosure

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**EP722**

A rare adventure of a lymphocytic hypophysitis

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Introduction

Lymphocytic hypophysitis is a rare endocrine disease involving lymphocytic infiltration and chronic pituitary inflammation. It may result in significant morbidity by loss of pituitary functions and neurological deficits. Pituitary abscess is another rare disease which may be associated with underlying parasellar pathology. Here, we report a case of lymphocytic hypophysitis diagnosed with a pituitary abscess and recurrent suprasellar involvement after surgery.

Case

A 58-year-old female presented with headache, panhypopituitarism and a pituitary lesion with thickening of pituitary stalk. A pituitary surgery was done for definitive diagnosis and it revealed pituitary abscess associated with lymphocytic hypophysitis. Four months after antiinflammatory treatment, the lesion recurred with extension to hypothalamus and compressive symptoms. High dose glucocorticoid treatment was initiated after exclusion of recurrent pituitary abscess with second surgery. The pituitary lesion reduced significantly in 3 months. However, the glucocorticoid treatment had to be stopped earlier due to toxic hepatitis and replaced to azathioprine.

Discussion

Lymphocytic hypophysitis may cause complete loss of vital pituitary functions and neurological deficits. The disease may rarely be complicated with abscess, therefore careful evaluation and surgical treatment should be performed in these cases. Most symptomatic LH require pulse doses of methyl-prednisolone or prednisone followed by a slow taper over a period of weeks to months. Despite good response to these first-line therapies in the majority of patients, relapses are common. In recurrent and symptomatic lymphocytic hypophysitis, high-dose glucocorticoids combined with azathioprine may be a successful choice of treatment.

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EP723 Determinants of neutrophil/lymphocyte ratio in acromegaly patients

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Introduction
Neutrophil/lymphocyte ratio (NLR) is an indicative of the acute phase response. It is a significant indicator of the systemic inflammation, and considered as a poor prognosis indicator in various disease. We aimed to evaluate NLR and its determinants in acromegaly patients.

Patients and methods
A retrospective chart review of 40 patients with acromegaly and 45 age and sex matched healthy individuals was performed. Patients with active infection, malignancy, chronic inflammatory or autoimmune disease, history of drug use or disease which may affect the hemogram values were excluded from the study. GH, IGF-I and hemogram values of patients were recorded and NLR was calculated. Correlation analysis was performed between GH, IGF-I levels and NLR.

Results
Mean age of the acromegalic patients was 47.68 ± 12.33 and the control group was 45.16 ± 6.63. NLR in acromegalics was 2.04 ± 0.63 and in the control group 1.88 ± 0.70. In terms of NLR, the difference between the two groups was not statistically significant (P = 0.075). When acromegalics were divided into active (n = 27) and controlled group (n = 13) no statistically significant difference was observed between all three groups (P = 0.204). NLR was 2.08 ± 0.70 in active group and 1.95 ± 0.45 in controlled acromegalics and the difference between the two groups was not statistically significant (P = 0.556). There wasn’t significant correlation between GH, IGF-I levels and NLR. Negative correlation was observed between age and NLR in acromegalics, especially the active acromegalics.

Conclusion
Cardiovascular disease is a major cause of morbidity and mortality in acromegaly patients. Studies reported an association between elevated NLR and increased risk of cardiovascular disease. We didn’t found an increase in NLR in acromegalic patients. Also in these patients, there wasn’t significant association between GH, IGF-I levels and NLR. However, in the literature we couldn’t find any study on this issue. Further studies are required in order to make adequate comment on this topic.

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EP725 Predictive factors for remission and recurrence in Cushing’s disease: a single-centre study

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Introduction
Cushing’s disease (CD) is characterised by pathologic hypercortisolism caused by an ACTH-secreting pituitary adenoma. The primary modality for definitive treatment is pituitary surgery. The rarity of CD has made it difficult to establish reliable predictive factors of outcomes.

Aim
Assessment of clinical, hormonal, radiological, surgical and histological findings as predictors of remission and relapse of CD.

Methods
Cross-sectional, retrospective study of patients with CD who underwent pituitary surgery between January/1998 and October/2013.

Results
45 patients were evaluated, 39 women (86.7%), with a mean age at diagnosis of 38.2 ± 12.9 years, and a mean follow-up of 90.4 ± 56.7 months. After surgery, 33 patients (73.3%) achieved cure, 12 patients (26.7%) presented persistent disease. Ten patients relapsed (30.3%), with mean follow-up time until relapse of 64.1 ± 36 months. There were no significant differences in urinary free cortisol, ACTH, serum cortisol and cortisol in the overnight dexamethasone suppression test at diagnosis between patients with and without disease remission after surgery, or between patients with and without disease recurrence. Morning serum cortisol (obtained from 36 patients) the day after surgery was 16.5 ± 18.3 μg/dl, with higher values in patients without cure in comparison with those in remission (27.6 ± 19.3 vs 12.2 ± 16.3; P = 0.043).

Conclusion
Serum cortisol measured at 24 h after pituitary surgery was not predictive of remission of CD. A longer interval between surgery and hormonal evaluation may allow a more accurate classification of these patients, including those with later remission.

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EP724 Serum cortisol in the early postoperative period as predictor of remission in Cushing’s disease

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Introduction
Pituitary surgery is currently considered the preferred treatment for Cushing’s disease (CD) and achieves remission in 55–85% of patients. Cortisol falls quickly after surgery, so that early post-operative cortisol level has been used as predictor of remission. There’s no agreement about optimal timing for cortisol measurement, with wide variability between centres.

Objective
To assess the value of early post-operative serum cortisol as predictor of remission after pituitary surgery in CD.

Methods
Cross-sectional, retrospective study of patients who underwent pituitary surgery for CD between January/1998 and October/2013. No glucocorticoid replacement therapy was initiated until blood samples were drawn (0800 h the day after surgery).

Results
We evaluated 45 patients, 86.7% (39) female, with a mean age of 38.2 ± 12.9 years at diagnosis. Mean follow-up was 90.4 ± 56.7 months. After surgery, 33 patients (73.3%) achieved cure, 12 patients (26.7%) presented persistent disease. Ten patients relapsed (30.3%), with mean follow-up time until relapse of 64.1 ± 36 months. There were no significant differences in urinary free cortisol, ACTH, serum cortisol and cortisol in the overnight dexamethasone suppression test at diagnosis between patients with and without disease remission after surgery, or between patients with and without disease recurrence. Morning serum cortisol (obtained from 36 patients) the day after surgery was 16.5 ± 18.3 μg/dl, with higher values in patients without cure in comparison with those in remission (27.6 ± 19.3 vs 12.2 ± 16.3; P = 0.043).

Conclusion
Serum cortisol measured at 24 h after pituitary surgery was not predictive of remission of CD. A longer interval between surgery and hormonal evaluation may allow a more accurate classification of these patients, including those with later remission.

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EP726
Effectiveness of somatostatin analogs as first-line or second-line treatment of acromegaly: single centre experience
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Introduction
The purpose of this study was to evaluate and compare disease outcomes in patients with acromegaly receiving first-line and second-line (after transphenoidal surgery) somatostatin analogs (SSA) treatment.

Methods
The study involved retrospective data collection from charts of 49 patients with acromegaly who were consulted by an endocrinologist in Vilnius University Hospital Santariskiu klinikos between 2007 and 2013.

Results
Patient population consisted of 16 males (32.7%) and 33 (67.3%) females (mean age at diagnosis 54 ± 13 years). Primary SSA therapy was administered in 14 (28.6%) patients who refused or had contraindications to surgical treatment. Transphenoidal operation was applied as the first-line therapy in 31 (63.3%) patients and led to disease remission in 16 (51.6%) of them. Of surgically treated patients, 15 (48.4%) were diagnosed with disease recurrence and received second-line SSA therapy. Based on the latest GH and IGF-1 results, control and partial control were achieved in 4 (28.6%) and 5 (35.7%) patients in first-line SSA therapy group, and in 7 (46.7%) and 4 (26.7%) patients in second-line SSA therapy group. 5 (35.7%) and 4 (26.7%) of patients in first-line and second-line SSA treatment groups remained uncontrolled. Although we observed higher mean observational period IGF-1 in the first-line SSA treatment group (511.0 (230.9; 791.1) μg/l) as compared to second-line SSA therapy group (403.3 (203.3; 526.2) μg/l), the difference was not statistically significant (P = 0.384).

Conclusions
SSAs are more effective in the treatment of acromegaly when applied after transphenoidal surgery, as they help to achieve control of the disease in a greater percentage of patients. Control of the disease remains a challenge despite availability of high-dose SSA treatment as 27–36% of patients receiving primary or second-line SSA treatment remain uncontrolled.

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EP727
The impact of diabetes mellitus on the survival of patients with acromegaly
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Aims
An increased risk of mortality in patients with uncontrolled acromegaly has been reported in several studies. We aimed to assess the impact of co-morbidities on the survival of patients with acromegaly after long-term treatment and follow-up.

Methods
A retrospective analysis was performed for 285 patients with active acromegaly who were admitted to the Chang Gung Memorial Hospital, Taiwan between 1978 and 2012.

Results
Of these patients, 106 (37.2%) were diagnosed with diabetes mellitus (DM). During the follow-up period, 21 cases of histological proved malignant in acromegalic patients, and DM with acromegaly had a higher incidence of malignancy (13.2% vs 3.8%; P < 0.01). The 5-, 10-, and 20-year survival rates were 93.1, 86.9, and 84.7% for the DM group, respectively, and 96.7, 96.7, and 96.7% for the non-DM group, respectively. After a mean follow-up of 15.1 ± 0.6 years, age, DM, coronary heart disease, and malignancy were found to be significant factors of mortality. Control of growth hormone and IGF-1 levels also conferred a marginal survival benefit.

Conclusions
DM and malignancy significantly influence the survival of patients with acromegaly; thus, these patients need close follow-up and appropriate therapy.

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EP728
Impact of gsp mutations in somatotroph pituitary adenomas on growth hormone response to somatostatin analogues: a meta-analysis
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Objective
Somatic mutations in the GNAS1 gene, which encodes the alpha-subunit of G stimulatory proteins (gsp), are frequently detected in somatotroph pituitary tumors and have been associated to specific clinical-smaller and less invasive tumors occurring in older patients- and histopathological-densely granulated adenomas- characterstics. However, the question whether the presence of a somatic gsp mutation affects the response to somatostatin analogue treatment remains unresolved.

Design
Following a literature search, we performed a meta-analysis, including eight eligible studies, in order to estimate the effect of gsp mutation on the percent reduction of growth hormone (GH) levels during an acute octreotide suppression test (OST). A total of 310 patients with acromegaly (126 gsp (+) and 184 gsp (−)) were included in the analysis.

Results
The presence of the gsp mutation was related with a greater reduction in GH levels on OST (weighted mean difference (WMD): 9.08% (95% CI, 2.73, 15.42; P = 0.005; random effects model). There was significant heterogeneity for this effect estimate (I² = 58%, P value for heterogeneity = 0.02). A sensitivity analysis after exclusion of a study with different methodology of OST provided similar estimates (WMD: 6.93% (95% CI, 1.40, 12.46; P = 0.01) albeit with no significant heterogeneity (I² = 35%, P value for heterogeneity = 0.16).

Conclusions
The present meta-analysis suggests a role for gsp mutation as a predictive factor of which patients with acromegaly are best candidates for treatment with somatostatin analogs. In order to further clarify this position, studies evaluating the long term effect of treatment, using the combination of GH and IGF-1 measurements are needed.

Disclosure
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EP729
Does cigarette smoking affect serum total cortisol and salivary cortisol levels?
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Aim
Although there are some studies regarding the effects of cigarette smoking on serum total cortisol (STC) and salivary cortisol (ScC) levels, the results are still challenging. For this purpose, we aimed to determine the effects of cigarette smoking on STC and/or ScC levels in a small group of healthy volunteers.

Study design
15 (five female and ten male) cigarette smoker with the mean age of 39.47 ± 14.27, and 15 age and gender matched non-smoker (mean age: 42.47 ± 13.46)
healthy people recruited to the study. Hypothalamo-pituitary-adrenal (HPA) axis was evaluated by basal STC and SaC levels, and STC and SaC responses to standard dose (250 µg) ACTH stimulation test. STC and SaC levels were obtained basal and stimulated conditions. Results Basal STC levels were statistically lower in smokers than non-smokers (8.41 ± 4.52 and 13.36 ± 6.68 µg/dl, respectively). Although peak STC were lower in smoker male group than non-smoker male group (30.41 ± 5.79 and 41.10 ± 12.87 µg/dl, respectively), SaC levels were not different (2.41 ± 0.31 and 2.16 ± 1.00 µg/dl, respectively). SaC levels were not affected by cigarette smoking in overall group or in the sub-groups of gender, either. Conclusion In our study, SaC levels were not found to be different in smoker group than non-smokers. Further studies including more subjects are needed. DOI: 10.1530/endoabs.37.EP729

**EP730**

**Evaluation of long term soccer player causing growth hormone deficiency: a pilot study**

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Objective Our aim was to evaluate whether multiple mild head trauma or repetitive heading of long term soccer playing causes growth hormone deficiency. Patients and methods 28 retired previously professional male soccer players were investigated. Nine of them had sport related head injuries. Mean age: 48.7 years (range 36–70; S.D. ± 7.4); mean sport duration (professional and senior activity): 27.4 years (S.D. ± 8.17). IGF-I, luteinizing hormone (LH), total testosterone (TT) and quality of life with the QoL–Assessment of Growth Hormone Deficiency in Adults (AGHDA) questionnaire were investigated. Results The mean IGF-I was 376.87 ng/ml (range 214.30–503.26 ng/ml S.D. ± 1.25; normal value 2.4 points (range 0–12 S.D. ± 0.74); mean sport duration (professional and senior activity): 27.4 years (S.D. ± 8.17). IGF-I, luteinizing hormone (LH), total testosterone (TT) and quality of life with the QoL–Assessment of Growth Hormone Deficiency in Adults (AGHDA) questionnaire were investigated. Results The mean IGF-I was 376.87 ng/ml (range 214.30–503.26 ng/ml S.D. ± 81.42), the mean IGF-I-s.d. score (SDS) value was 2.19 (range 0.74–3.02). The mean LH was 85.9 vs 368.41 ng/ml (S.D. ± 0.31; normal range: 57.9–12.07), mean TT was 17.44 nmol/l (S.D. ± 1.19), in TT (16.64 nmol/l (S.D. ± 2.74), in IGF-I-SDS (2.23 vs 2.13), in LH (3.36 G 1.00) and in QoL-AGHDA scores (3.23).

Conclusions There was no difference between normal populations and retired soccer players in IGF-I SDS values, LH, TT levels and QoL–AGHDA scores. The results suggest that long term soccer playing does not damage the most vulnerable pituitary hormone secretion. Although the dynamic tests (e.g. insulin tolerance test) in a larger population would result more reliable data, but according to our pilot study the consequence of these dynamic investigations are ambiguous. Disclosure IPSEN Pharma Hungary, Novo Nordisk Hungary DOI: 10.1530/endoabs.37.EP730

**EP732**

**Efficacy and safety of tolvaptan in treatment of SIADH; case-series from 2 UK hospitals**

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Introduction Contrary to US guidelines, recent European guidelines do not recommend tolvaptan for the treatment of SIADH. Methods Retrospective data collection of all inpatients treated with tolvaptan for SIADH in two UK hospitals between November 2010 and February 2014. All values were calculated as mean ± s.d.

Results This case series included 61 patients (33 females, 28 males) aged 74.4 ± 15.3 years with serum sodium (sNa) 119.9 ± 5.5 mmol/l. The aetiology of SIADH was malignancy (24.6%), unknown (24.6%), pulmonary (14.7%), neurosurgical (11.5%), drug-induced (9.8%), post-operative (9.8%) and various (5%). Initiation tolvaptan dose was 15 mg in 55/61 and 7.5 mg in 6/61 cases. 24 h after administration of tolvaptan, sNa increased by 9 ± 5.9 mmol/l; specifically, 2–8 mmol/l in 45.9%, 9–10 mmol/l in 16.4%, 11–12 mmol/l in 19.7% and > 12 mmol/l in 18% of patients. Overcorrection, defined as sNa increase of > 12 mmol/l in 24 h or > 18 mmol/l in 48 h, was observed in 22.3%, while increase of > 10 mmol/l in 24 h occurred in 39.3% of patients. No patients developed osmotic demyelination syndrome. None of 12 patients with baseline sNa ≥ 125 mmol/l exhibited increase > 10 mmol/l in 24 h. The duration of tolvaptan use was 4.2 ± 4 days. At the end of tolvaptan therapy, sNa increased by 13.2 ± 5.9 mmol/l with only 26/1 (3.5%) ‘non-responders’, having sNa increase ≤ 5 mmol/l or sNa ≤ 130 mmol/l. Five days after withdrawal of tolvaptan, mean change of sNa was −3.8 ± 6.6 mmol/l with sNa reduction by ≤ 5 mmol/l in 21/50 (42%) patients. Conclusions Tolvaptan is effective, but can often lead to overcorrection of hyponatraemia. Physicians should monitor closely sodium levels and take appropriate measures to prevent or reverse overcorrection, especially in patients with baseline sNa ≤ 125 mmol/l. DOI: 10.1530/endoabs.37.EP732

**EP733**

**Evaluation of GH secretion after stroke**

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Carney complex (CNC) is rare autosomal dominant disorder, which was firstly described as a combination of manifestation of myxomas, spotty skin pigmentation and endocrine overactivity in 1985. This condition affects many organs and varies in clinical manifestation. The presence of at least two clinical signs is considered as pathognomonic with regard to a sporadic form of CNC, and an evidence of at least one sign with simultaneous manifestation of CNC in any of first degree relatives is considered as pathognomonic with regard to a familiar form. Intracardiac and extracardiac myxomas are the most common diagnostic signs. In our report, we present a case of 36-year male patient with history of surgery for testicular Sertoli – cell tumour and surgery of thyroid nodule, with diagnosis of acromegaly. The patient was examined for persistence of hypercortisolism after partial resection of growth hormone secreting pituitary adenoma, followed by radiation treatment with Leksell γ knife and treated by somatostatin analogues. Recently, as a part of differential diagnosis procedure aiming to discover other increased endocrine activity, we consider potential occurrence of intermittent hypercortisolism based on primary pigmented nodular adrenocortical disease. As a part of comprehensive examination of associated complications of acromegaly we added echocardiography with findings of intracardiac tumours. Drifting thrombus, or bacterial flora, or myxomas were considered as options in differential diagnosis. Patient underwent urgent surgical excision of myxomas in left and right atrium at Cardiac Surgery Clinic. The diagnosis of Carney complex was confirmed by genetic testing. DOI: 10.1530/endoabs.37.EP731
Objective
According to recent studies, impaired secretion of GH is a frequent finding after ischaemic stroke. The aim of our study was to compare various available GH stimulation tests in post-stroke patients.

Design
Seventeen patients were included in the study (12 males; mean age: 46.6 ± 9.9 years; mean BMI: 27.7 kg/m²) with a mean 19.6 (±7.3) months after stroke. For screening, glucagon and small dose (0.15 μg/kg) GHRH-arginine (sdGHRH-A) stimulation tests were carried out in consecutive days. If either or both of them were abnormal, a large dose (1 μg/kg) GHRH-arginine (ldGHRH-A) stimulation, as a standard confirmatory test was carried out, as well.

Results
Maximum GH values reached in sdGHRH-A and glucagon stimulation tests were strongly correlated to each other (r = 0.943; P < 0.001), but neither showed association with ldGHRH-A results. Furthermore, IGF-I levels did not correlate with stimulated peak GH values received in any of the three tests. Comparing diagnostic interpretations of stimulation tests to each other, considerable discrepancies were detected in all directions, partly due to various cut-off values of the applicable criteria.

Conclusions
Adequate GH secretion is common after stroke. If this indication was being included in the screening for GH insufficiency, a larger trial is warranted to evaluate which tests are appropriate because a single GH stimulation test may not necessarily be enough in this population.

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EP735
Aetiology of hypopituitarism in adult life: last 10 years' experience in single centre database in Serbian population
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Hypopituitarism as deficiency of one or more anterior pituitary hormones, in adults can be consequence of acquired or genetic causes. Only few published studies investigated population-based aetiology of hypopituitarism. In the last 10 years new risks for hypopituitarism have been recognised (traumatic brain injury-TBI, subarachnoid haemorrhage, cranial irradiation).

Aim
To present our experiences in the aetiology of hypopituitarism based on data collected during last 10 years in Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Centre of Serbia. This is a single centre cross-sectional database study.

Patients
A total of 426 patients with hypopituitarism were included, mean age 44.6 ± 0.8 years (range 16–82), male 60.3%. The mean age at diagnosis of hypopituitarism was 37.7 ± 1.2 years. Inclusion criteria were: patients older than 16 years, hypopituitarism confirmed by endocrine assessment of pituitary function and MRI of the sellar region. Results are expressed as mean ± SE and percentages (%).

Adult onset of hypopituitarism (AOGHD) is reported in 73% pts, while childhood onset of hypopituitarism (COGHD) in 27% pts.

Results
The most common causes of hypopituitarism are: nonfunctional pituitary adenoma (160 pts, 37.6%), followed by congenital causes (66 pts, 15.5%). Acromegaly and prolactinomas are present in 30 pts (7.0%) each, followed by craniohypophysealomas (28 pts, 6.6%). TBI was the cause of hypopituitarism in 19 pts. (4.5%). Other aetiologies are reported in less than 4% in each category.

Conclusion
Our results show that aetiology of hypopituitarism may depend on the period of time study. Our transition clinic with paediatric endocrinologists in the last years influenced high prevalence of congenital hypopituitarism. Similarly our database confirms that patients with brain damage either by traumatic brain injury or cranial irradiation are at high risk for hypopituitarism.

Disclosure
This work was supported by the Serbian Ministry of Science (project number 175033).

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EP736
Persistent hyponatremia in patient with acromegaly, congestive heart failure and diabetes insipidus
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Introduction
Increased production of vasopressin plays a key role in the development of fluid retention and hyponatremia in patients with decompensated heart failure. Antidiuretic hormone deficiency in the course of diabetes insipidus leads to the loss of water, dehydration and hyponatremia. The aim of the study was to present difficulties in successful treatment of hyponatremia in a patient with cardiomyopathy and heart failure, receiving desmopressin because of post-operative diabetes insipidus.

Case report
70-year-old man with somatic features of acromegaly, after transphennoidal surgery proper pituitary microadenoma (7.2 mm). Postoperative histopathological examination showed pituitary adenoma, ACTH (−); TSH (−); FSH (−); PRL (+), GH (−). He developed post-surgical pituitary insufficiency requiring long-term substitution of hydrocortisone, thyroxin, testosterone and desmopresin. Before the diagnosis of acromegaly, the clinical picture was dominated by symptoms of cardiomyopathy. After surgery there was an improvement of heart failure, lasting for about 8 years. 4 years ago the worsening of heart failure

Disclosure
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appeared with an increased atrial natriuretic peptide ranging from 701–2358 pg/ml. Between 2010-2011 the patient was hospitalised eight times in cardiovascular and endocrinological departments because of circulatory decompression and severe hyponatraemia (118–120 mmol/l). Dilated cardiomyopathy was diagnosed with insufficiency of mitral valve III, tricuspid valve III, aortic valve II and congestive heart failure NYHA II/III. Substitution of adrenal and thyroid insufficiency was correct. In October 2011, after a withdrawal of desmopressin, normalisation of sodium levels and improvement of heart function persisting up to now were achieved.

Conclusion
An improvement of heart failure and normalization of blood natriemia after the desmopressin withdrawal may suggest the regression of diabetes insipidus in our patient (9 years after an operation?), or, what is more likely, the beneficial influence of partial deficiency of antidiuretic hormone on reduction of the retention of body fluids and cardiovascular efficiency.

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EP737
Clinical features of pituitary adenomas in elderly patients in Castilla La Mancha (Spain) compared with younger age group; a retrospective multicentre study
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Background
Pituitary adenomas (PAs) in the elderly, defined as people older than 65 years, represent less than 10% of all PAs. Because of increasing life expectancy and improving health care, diagnosis PAs in this age group is increasing with time. Age-related changes and associated diseases may significantly modify the clinical presentation in these patients, delaying the diagnosis of PAs.

Objective
To analyse the clinical features of PAs in elderly patients in a study population from Castilla – La Mancha (Spain).

Design
Retrospective observational study.

Methods
The study included 346 patients with a presumptive diagnosis of pituitary adenomas between 2000 and 2012. Review of medical records of elderly patients with PAs was carried out.

Results
67 patients, 19.4% of whole PAs, were studied (62.7% women). Mean age was 73 years (range 65–87). At presentation, visual impairment, headache and hypersomatotropism and severe hyponatraemia (118–120 mmol/l). Substitution of adrenal and thyroid insufficiency was correct. In October 2011, after a withdrawal of desmopressin, normalisation of sodium levels and improvement of heart function persisting up to now were achieved.

Conclusion
An improvement of heart failure and normalization of blood natriemia after the desmopressin withdrawal may suggest the regression of diabetes insipidus in our patient (9 years after an operation?), or, what is more likely, the beneficial influence of partial deficiency of antidiuretic hormone on reduction of the retention of body fluids and cardiovascular efficiency.

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EP738
Obstructive sleep apnoea is common in patients who have had surgery for non-functioning pituitary adenomas; preliminary data
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Introduction
Some patients complain of excessive daytime somnolence following pituitary surgery.

Aim
To investigate the presence of obstructive sleep apnoea (OSA) following surgery for non-functioning pituitary adenomas (NFPA).

Design and methods
We assessed the prevalence of OSA in 16 routinely selected patients following surgery for NFPA and 13 obese controls attending a tertiary referral centre, by means of the Epworth Sleepiness Score (ESS) and polysomnography. All subjects with sleep apnoea were offered continuous positive airway pressure therapy (CPAP).

Results
The median age in NFPA group was 60 years (IQR: 51, 67) vs 49 years (IQR: 43, 56), p = 0.025. Gender: Male: 9/16 (56%) in NFPA vs 7/13 (54%) in control group, P = 0.89. 15/16 (93%) patients had postoperative hypopituitarism and were on appropriate hormone replacement at the time of evaluation. Median ESS was 13 (IQR: 5.25, 36) in NFPA patients and 5.7 (1.75, 18.55) in controls, P = 0.04. 14/18 (87%) NFPA patients had apnoea hypopnoea index (AHI) > 5, compared to seven patients (53%) in the obese control group, P = 0.043, with 10/15 (66%) with complete anterior pituitary failure. 9/10 (90%) patients with complete anterior pituitary failure were diagnosed from OSA (AHI > 5) and were started on CPAP. There were no statistically significant differences in the prevalence of OSA in patients with complete anterior pituitary failure after surgery (90%) compared to those with partial anterior hypopituitarism 4/6 (66%), P = 0.24. BMI did not correlate with apnoea hypopnoea index (apnoea – hypopnoea index (AHI), r = 0.17, P = 0.54), which suggests that factors other than obesity might explain the prevalence of sleep apnoea after surgery in patients with NFPA.

Conclusions
OSA is common following surgery for NFPA, and is not explainable solely by associated obesity. Polysomnography should be offered to NFPA patients with somnolence or symptoms of OSA.

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EP739
Mean platelet volume in patients with prolactinoma
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Introduction
Prolactin is a multifunctional pituitary hormone. The effect of prolactin on platelet activation is not well understood. Prolactinomas are the most common type of pituitary adenomas, and they are medically responsive to dopamine agonists. Mean platelet volume (MPV) is a marker of platelet function and activation. The aim of this study was to evaluate MPV values before and 6 months of cabergoline treatment when normoprolactinemia was achieved.

Methods
A total of 101 newly diagnosed prolactinoma patients and 102 healthy control subjects were included in the study. Patients with haematological disorders that affect MPV and those on medications were excluded. Prolactin, platelet count and MPV levels were recorded before and 6 months after the initiation of cabergoline treatment (0.5–1 mg, two times a week).

Results
There was no significant difference in platelet count and MPV before and after 6 months of treatment with cabergoline in patients with prolactinoma compared with the control group (P > 0.05).

Conclusion
Our results showed that MPV, a marker of platelet function, was unchanged in patients with prolactinoma.

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EP740

Differentiated thyroid cancer in patients with prolactinoma
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Introduction
Increasing evidence is available for the role of prolactin in the development of various cancers. The purpose of this study is to evaluate the frequency of thyroid cancer in patients with prolactinoma followed up at a single site.

Materials and methods
Medical records of 182 patients, diagnosed with prolactinoma, were reviewed retrospectively. Out of these patients, 114 patients (103 female patients, 11 male patients, mean age 35±10.4, who had undergone thyroid ultrasonography (US), were included in the study. Serum prolactin, anti-thyroglobulin (anti-Tg), anti-thyroid peroxidase antibody (anti TPO), thyroid stimulating hormone (TSH), free T₄ (fT₄), free T₃ (fT₃) values, and pituitary gland magnetic resonance imaging (MRI) and US reports were evaluated.

Results
It was found that 45(39.5%) patients had thyroid nodule (13 solitary, 32 multiple). ten patients were administrated thyroidecotomy, and differentiated thyroid cancer (DTC) was detected in six of these patients (5.3%). One patient had lung metastasis. Control group consisted of 113 individuals (101 females, 12 males, mean age 32.1±9.1). In US, 28 of these individuals (24.8%) had thyroid nodule (five solitary, 23 multiple). One individual (0.8%) had DTC.

Conclusion
When compared to control group, thyroid volume and thyroid nodularity were significantly higher in patients with prolactinoma (respectively, P<0.001, P=0.0186), however, no statistically significant difference was available for the incidence of thyroid cancer (P=0.196).

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EP741

Squamous cell carcinoma of the sphenoid sinus presenting as a sellar mass
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Introduction
We present a rare case of squamous cell carcinoma of the sphenoid sinus presenting as a sellar mass and panhypopituitarism.

Case presentation
A 60-year-old Chinese male with schizophrenia and a 20 pack year smoking history, was admitted to our hospital with headache and diplopia without visual field loss. Brain imaging with computed tomography (CT) and magnetic resonance imaging (MRI) revealed a 2.9 cm sellar mass based in the sphenoid sinus, bulging into the suprasellar cistern with post contrast enhancement and pituitary stalk thickening. The optic chiasma was indented, with involvement of the cavernous sinuses and superior portion of the clivus. Subsequent hormonal investigations revealed panhypopituitarism (central hypogonadism, hypothyroidism and hypercortisolism) with hyperprolactinaemia likely from pituitary stalk occlusion and compression and anti-psychotic medication. There were however no symptoms of central diabetes insipidus (DI). Hormonal replacement with oral hydrocortisone and thyroxine was commenced. An initial biopsy showed focal moderate to severe keratinising dysplasia but no definite invasive malignancy, and a repeat biopsy was planned. Repeat imaging done for worsening symptoms 2 weeks later showed an increase in the size of the sellar mass to 4 cm. Trans-sphenoidal debulking surgery was carried out, and intra-operative biopsy and frozen section revealed the diagnosis of squamous cell carcinoma. Staging CT scans did not reveal any lymph node or distant metastases. Post operatively, patient developed central DI with a biphasic pattern. In view of the advanced intracranial involvement of the tumour, palliative chemotherapy and radiotherapy was planned but patient unfortunately developed progressive worsening neurological deficits likely from tumour progression and passed away.

Conclusion
Squamous cell carcinoma of the sphenoid sinus can rarely present as a sellar mass. Although pituitary adenoma are the most common cause of sellar masses, atypical features such as pituitary stalk thickening or central DI necessitate a high index of suspicion to look for other causes.

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EP742

Tumour regrowth in growth hormone deficient adults with non-functioning pituitary adenomas using growth hormone replacement therapy – a sub-analysis from the Dutch National Registry of growth hormone treatment in Adults
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Objective
Growth hormone treatment (GHT) is a widely accepted treatment in growth hormone deficient (GHD) adults with nonfunctioning pituitary adenoma (NFPA).

Introduction
Increasing evidence is available for the role of prolactin in the development of thyroid cancer in patients with prolactinoma. Therefore, we aimed to determine the incidence of thyroid cancer in patients with prolactinoma followed up at a single site.

Results
There were 182 patients, mean age 35.5 years, BMI was 27.7 (±5.3) kg/m². Time since diagnosis was 30.6 (±17.8) months. Acromegaly was most frequently diagnosed by endocrinologists.
(29.5%) and general practitioners (16.1%). GH- and GH/PRL-secreting pituitary adenomas were reported in 78.8% and 18.2% of patients, respectively. Most patients had a macroadenoma (80.3%). At diagnosis, GH level was 18.7 (±30.1) μg/l and IGF1 level was 295 (±160) μg/l. Among patients with GH/PRL adenoma, serum prolactin level was 183 (±650) μg/l.

At diagnosis, patients presented morphological signs ( coarse facial feature, enlargement of hands and feet) (96.2%), skin manifestations (85.8%), respiratory problems (83.5%), asthma (79.2%), osteoporosis (76.1%), endocrine complications (73.3%), tumor mass effects (69.1%), weight gain (64.6%), cardiovascular diseases (62.9%), ear-nose-throat disorders (62.1%), carpal/cubital tunnel syndromes (58.1%), gastrointestinal symptoms (57.8%), sexual dysfunctions (47.7%), metabolic abnormalities (42.8%) (diabetes mellitus (27.5%), impaired glucose tolerance (9.5%), psychologic changes (28.8%), and malignant diseases (11.9%). Overall, mean time between symptom or comorbidity onset and diagnosis of acromegaly was 5.1 (±4.3) years.

Conclusion

This study provides insights on symptoms and comorbidity of acromegalic patients recently diagnosed. Results confirm the broad range of comorbidities at diagnosis and the delay for the diagnosis of acromegaly, and therefore emphasise the efforts needed in improving the early recognition of the disease.

Disclosure

Grant from Ipsen Pharma SAS.

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EP744

Symptoms of gonadal dysfunction are more predictive of hypopituitarism than non-specific symptoms in screening for pituitary dysfunction following moderate or severe traumatic brain injury

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Context

The economic and logistic burden of screening for hypopituitarism following moderate/severe traumatic brain injury (TBI) is considerable. Published guidelines suggest prioritisation for screening of patients with symptoms of pituitary dysfunction.

Objective

To evaluate the implementation of targeted symptom-based screening for hypopituitarism following moderate/severe TBI, compared with routine consecutive screening.

Design

Group 1 (G1); consecutive patients were screened. Group 2 (G2); screening targeted based on symptoms of pituitary dysfunction. Setting: G1 patients were recruited from the Irish National Neurosurgery Centre and in G2 on symptom based referral from external caregivers. Patients: G1, 137 patients (113 male) and G2 111 patients (77 male) referred for pituitary evaluation (G2).

Main outcome measures

The rate of pituitary hormone deficiency between groups.

Results

Patients with menstrual dysfunction (n=10) had more GH (50% vs 11%, P=0.001), ACTH (60% vs 14%, P<0.0001) or gonadotrophin (90% vs 16%, P<0.0001) deficiency and any pituitary hormone deficit (100% vs 33%, P<0.0001) than G1. Men with symptomatic hypogonadism (n=12) had more GH (53% vs 11%, P=0.03), gonadotrophin (58% vs 16%, P<0.0001) and TSH (16% vs 1%, P=0.03) deficiency than G1. Patients with non-specific symptoms (n=89) were no more likely to have hypopituitarism than those consecutively screened. The rates of GH (19% vs 11%, P=0.12), ACTH (14% vs 14%, P=0.99), TSH (3% vs 1%, P=0.34), ADH (7% vs 2%, P=0.44) or any pituitary hormone deficit (25% vs 33%, P=0.21) were not different between those referred with non-specific symptoms in G1 and G2.

Conclusions

Symptoms of hypogonadism are sufficiently predictive of hypopituitarism to justify inclusion in protocols for screening for hypopituitarism following moderate/severe TBI. Non-specific symptoms of hypopituitarism are no more predictive than systematic screening in identifying pituitary hormone deficits: their place as indicators for screening is therefore questionable.

EP745

A 5 years retrospective studies looking at trends in water deprivation tests and roles for endocrine specialist nurses

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Performing water deprivation test (WDT) and prolonged water deprivation test (PWDT) is some of the roles undertaken by endocrine nurse in specialist endocrine units. These tests need to be done in a safe and control environment.

Objectives

To provide safe information to patients to avoid fluids overload when they arrive for the tests. Can the specialist endocrine nurse make clinical decision to terminate the test base on clinical evidence and at what point the communication with consultant is crucial in order to collect results of clinical relevance?

Methodology

35 patients who completed WDT and PWDT over the last 5 years were studied. Results

Three with overt normal (ON), five with normal (N), three with nephrogenic diabetes insipidus (NDI), 14 with cranial diabetes insipidus (CDI), two with primary polydipsia (PP), eight were excluded due to inability to complete their tests or lack of diagnosis and medical information. ON has the highest mean urine/sodium osmolality ratio at begin and termination of tests. Delay DDAVP during WDT is useful in some cases.

ADH measurement at Peak urine osmolality can be used to distinguish NDI from CDI. Primary Polydipsia urine/sodium osmolality Ratio increase according to the length of fluid fasting.

Conclusions/recommendations

Address fluids overloading with patients who are coming for these tests. The length of fluids fasting before these tests will be based on patient’s symptoms.

Endocrine specialist nurse can make clinical decisions if the tests are overtly normal or serum osmolality goes above 305 mOsm/kg. Additional markers such as ADH and serum sodium can be useful if needed at certain point during the tests.

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EP746

The effect of intra-articular glucocorticoid injections on hypothalamic-pituitary-adrenal-axis function: a review

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Background

The use of intra-articular (IA) glucocorticoids for reducing pain and inflammation in patients with osteoarthritis, rheumatoid arthritis, and other inflammatory arthropathies is widespread among primary care physicians, specialists and non-specialists in the United States. Injectable glucocorticoids have anti-inflammatory and analgesic properties which can be effective in improving clinical parameters such as pain, range of motion, and quality of life. After injection into the IA space, glucocorticoids may be systemically absorbed; the degree of absorption can depend on the size of joint injection, the preparation used, the dosage and frequency of injection. The adverse effects of IAGC can often be overlooked by both the patient and physician who administer them, in particular the potential deleterious effect on the hypothalamic-pituitary-adrenal (HPA)-axis which can result in adrenal suppression and/or iatrogenic Cushing syndrome.

Aim

We provide an overview on the often under-recognised effects of IAGC on HPA-axis function.

Disclosures

The work in this study was supported by unrestricted grants from Pfizer Pharmaceuticals and Novo Nordisk Pharmaceuticals.

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Results and conclusions
IAGC can result in a sharp decline in cortisol to low or undetectable levels within the first days after administration. HPA-axis suppression can typically last for up to 4 weeks after a single injection, although recovery of HPA-axis to baseline can take longer depending on the dose and frequency of injections. Considering the widespread use of IA steroid injections and their clinical effectiveness, physicians who administer them need to be aware of the potential risks of HPA-axis suppression and/or iatrogenic Cushing syndrome. Guidelines for the frequency of dosing in addition to defined time intervals between each injection should be clear. High risk populations have the potential to be screened for adrenal suppression and could include those who receive high doses and multiple injections particularly within the previous 6 months. The potential use of the measurement of salivary cortisol in identifying patients who have subtle changes in HPA-axis function remains to be seen.

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EP747
Prolactinomas: do age and gender affect clinic?
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Objective
To study the effect of age and gender on manifestation of hyperprolactinemia.

Methods
Patients were examined using generally accepted methods of diagnosis. 207 patients with prolactinomas were divided into two groups: before and after 50 years. It was a retrospective study with no interventions to generally accepted methods of diagnosis and treatment. The outcomes were measured by frequency of hyperprolactinemia symptoms according to age and gender.

Results
In patients who are <50 years prolactinomas were observed in 91% of women and 9% of men. The main clinical symptoms in women and men were presented by hyperprolactinemic hypogonadism. Menstrual irregularities were observed in 70% of women, galactorrhea – in 54%, infertility – in 53%. Macroadenomas were detected in 13% of women. Clinical signs of hypogonadism in men were presented by decreased libido (100%), erectile dysfunction (80%), infertility (6%) and depression (98%). Macroadenomas were diagnosed in 58% of men. In group over the age of 50 years prolactinomas were diagnosed in 61% of women and 39% of men. Clinical manifestation of the disease, both in women and men, was presented by neurological symptoms: headaches – in 86% of women and in 79% of men; visual disturbances – in 56% of women and 78% of men. Macroadenomas were detected in 68% of women and 89% of men.

Conclusion
People of reproductive age developed typical clinical picture of hyperprolactinaemic hypogonadism, which is well recognised in women, while often ignored in men. The frequency of macroadenomas with chiasmatic syndrome increases in both sexes over the age of 50 years, that is partly due to the lack of vivid clinical signs of hyperprolactinemia in the period of menopause.

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EP748
Body weight changes in patients with active Cushing disease after transsphenoidal surgery
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Background
Successful pituitary surgery in patients with Cushing disease (CD) can result in long term remission and sustained weight loss. We examined rates of body weight changes in the post-operative period (within 6 months) in patients with active CD who underwent transsphenoidal surgery (TSS) and the relationship of weight loss to remission status.

Method
Clinical data was obtained from a CD database in addition to an online patient medical record (EPIC). All patients with biochemically confirmed active CD underwent their first TSS by a single neurosurgeon at the Cleveland Clinic (October 2004–August 2013). No patients received glucocorticoids during surgery. Initial remission was defined by nadir cortisol <3 ng/dl, ACTH <5 pg/ml within the immediate post-operative period (72 h). Long term remission was defined as 24 h UFC <ULN (upper limit of normal), and/or sequential midnight salivary cortisols <ULN, and 1mg DST cortisol <1.8 µg/dl. Results
88 patients (female: 63, male: 25), with a mean age at presentation of 47 years (range 24-87 years), median follow up 52 months (12-118 months) underwent TSS. No significant differences in baseline demographics including pituitary adenoma size (P=0.25) and BMI (P=0.21) were observed between the two groups, 64: pituitary microadenoma, 24: macroadenoma. 74 (84%) patients had initial remission after surgery, during follow up six out of those with initial remission had recurrence. Those with initial remission had greater mean ± s.d. weight loss at 3 months (kg: –8.1 ± 11.3 (initial remission, n=59) vs 0.8 ± 8.8 (non-remission, n=12), P=0.007) and at 6 months (kg: –14.5 ± 12.1 (initial remission, n=46) vs –6.1 ± 12.1 (non-remission, n=12), P=0.045). Less weight loss or weight gain at three (P=0.005) and six (P=0.014) months was associated with increased relapse risk.

Conclusion
After TSS for CD, weight loss within the first 6 months is an additional early clinical indicator associated with initial biochemical remission.

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EP749
The development and validation of a new burden and needs assessment questionnaire for patients with pituitary diseases: the BNQ-Pituitary
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Background
An increasing number of studies assess quality of life (QoL) in patients with pituitary diseases. At present, available disease-specific QoL questionnaires do not completely cover the patient perspective of QoL. Furthermore, there are no disease-specific questionnaires available which inventories patient’s needs for help for impairments in QoL.

Objective
To develop and validate a disease-specific QoL questionnaire for patients with pituitary diseases based on the patient perspective on QoL, which also incorporates the needs for help: the burden and needs assessment questionnaire (BNQ-Pituitary).

Methods
337 patients with pituitary diseases fill-out the BNQ-Pituitary and eight other psychosocial questionnaires (i.e. EuroQol-5D, SF-36, HADS, UCL, GSE, IPQ-brief, IPA). Items were formulated based on results of a recent focus group study of our department. Construct validity was examined by using an exploratory factor analysis with oblique rotation on principal components. Reliabilities were calculated with Cronbach’s α and concurrent validity was measured by calculating Spearman correlations between BNQ-Pituitary reported burden and subscales of the other questionnaires.

Results
The exploratory factor analysis revealed seven subscales (i.e. Mood, Cognitive functioning, Illness perceptions, sexual functioning, social functioning, anxiety, physical complaints) containing a total of 33 items. Subscales reliabilities were all >0.736 and strong and consistent correlations were observed between BNQ-Pituitary scores and scores on the other psychosocial questionnaires. A significant effect of type of pituitary disease was observed, with patients with Cushing’s disease reporting the highest burden compared to patients with prolactinoma or non-functioning pituitary adenoma.

Conclusion
The BNQ-Pituitary is a valid and reliable instrument to measure not only the burden of pituitary disease, but also the need for help considering the consequences of the disease. Furthermore, the BNQ-Pituitary can facilitate the efficient assessment of patients’ unmet needs. We postulate that paying attention to potential unmet needs may positively affect QoL.

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EP750
Rate of Prolactin suppression can predict future prolactin normalisation, tumour shrinkage and time to remission in male macroadenomas
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Introduction
Dopamine agonists are the mainstay treatment for prolactinomas, but clinical characteristics that predict their effects on prolactin (PRL) suppression and tumour shrinkage are missing. Our study aimed to find measures in early follow-up of men harbouring macroadenomas, that will predict dynamics of PRL decrease and adenoma shrinkage.

Methods
A single centre historical prospective study, including a consecutive group of 71 men with pituitary macroadenomas (≥10 mm) and hyperprolactinaemia (>7xULN), treated medically with cabergoline. Comparisons of PRL normalisation rates were performed according to PRL levels achieved at 6 months, maximal adenoma shrinkage during follow-up, and other patient characteristics.

Correlations were performed to identify characteristics of PRL suppression dynamics. Results
Four patients had nadir PRL levels ≥3 xULN (51ng/ml), and showed slower response to treatment with cabergoline with consistently higher PRL levels compared to other patients throughout follow-up (6 months mean PRL levels, 519±403 vs. 59±118 ng/ml, P<0.001). PRL levels after 6 months of treatment correlated positively with current PRL levels (r=0.74, P<0.001), with adenoma diameter following treatment (r=0.38, P<0.01), and with time to PRL normalisation (r=0.75, P<0.001). Shrinkage of adenoma size depicted by first MRI on treatment correlated with maximal adenoma shrinkage during follow-up (r=0.56, P=0.006).

Conclusions
Six months PRL level might serve as a surrogate marker for PRL normalization and adenoma shrinkage dynamics among men harbouring macroadenomas.

Among these patients with persistent hyperprolactinaemia at 6 months, higher PRL levels are associated with resistance to cabergoline.

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EP751
Endonasal endoscopic pituitary adenoma resection
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Introduction
In the past 10 years, endoscopic resection of pituitary adenomas has become an alternative to microsurgical resection with the additional advantage of increasing the patient’s postoperative comfort. This analysis explored whether endoscopic resection can reduce the risk of postoperative neurohypophyseal dysfunction.

Material and methods
We rated and compared the need to administer desmopressin during the first four postoperative days and with the need after a follow-up of at least 3 months (chronic administration). Two groups of patients were compared: Patients in group 1 were operated on microsurgically. Patients in group 2 were operated on endoscopically. Group 1 was made up of 50 patients treated in 1999, group 2 comprised 50 patients operated on from 2006 to 2007.

Results
In group 1 the need to use desmopressin postoperatively occurred in eight patients: three needed chronic treatment. In group 2 the need for postoperative application of desmopressin occurred in four patients, none required chronic treatment.

Conclusions
Endoscopic surgery is a safe and effective method for the resection of pituitary adenomas. The rate of chronic desmopressin application was reduce.

Disclosure
NT13631-4.

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EP752
The comparison of echocardiographic parameters, carotid intima thickness, arterial stiffness and plasma soluble CD40 ligand levels in active and inactive acromegalic patients
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Introduction
In acromegalic patients, the increased mortality and morbidity are generally due to cardiovascular, metabolic, respiratory and cerebrovascular diseases, so early diagnosis and treatment of cardiovascular lesions may save lives. The aim of this study is to find out the any possible difference in terms of carotid intima media thickness (CIMT), indices of arterial stiffness, soluble CD40 ligand (sCD40L) and some echocardiographic parameters between active and inactive acromegalic patients.

Methods
The study involved 26 active, 24 inactive acromegalic patients and 20 healthy subjects. 47 of 50 acromegalic patients had undergone transsphenoidal surgery and 41 of 50 patients were using somatostatin analogues at least 6 months and nine patients have no treatment after transsphenoidal surgery. CIMT, arterial stiffness, sCD40L and some echocardiographic parameters were compared.

Results
The study showed that CIMT and indices of arterial stiffness were higher in acromegalic group (P=0.003 and P=0.008 respectively). Left ventricular diastolic dysfunctions were comparable between groups, whereas the left ventricle mass index, DOPPETI and left atrial diameter were higher, and ejection fraction was lower in acromegalic patients. CIMT, arterial stiffness, sCD40L and parameters of echocardiography were comparable in patients with active and inactive patients.

Discussion
Getting the disease under control hormonally didn’t cause a reduction in the subclinical cardiovascular risk. This can point out that in acromegalic patients the structural and functional damage may be due to long-term exposure to excess growth hormone/IGF1.

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EP753
An audit of transsphenoidal surgery on nonfunctioning pituitary adenomas
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Introduction and objective
Clinically nonfunctional pituitary adenomas are relatively an uncommon disease. The aim of this work is to describe the clinical characteristics and to review the results of transsphenoidal surgery (TS) of pituitary adenomas in a reference centre.

Methods
A retrospective study (1995–2014) of 66 patients (50% men) diagnosed with pituitary adenomas by a magnetic resonance imaging (MRI) was conducted. Demographic, clinical, biochemical data and the results of TS were collected. For statistical processing program SPSS version 22.0 was used.

Results
The mean age of the patients was 57±16.8 years. The most frequent clinical presentations were as an incidental pituitary mass (34.8%) and visual symptoms (36.4%). The mean size of the sellar tumour was 26.6±8.8 mm. A 59% of them had pathological visual field testing (34.8% bitemporal hemianopia). Some hormone deficiency was found in 66.7% of patients before surgery (16.7% of them presented panhypopituitarism). 52 out of 66 were referred for surgery, 49 because of the optic chiasm compression and three due to pituitary apoplexy. The mean size of the tumour was 28.55 mm in those who underwent surgery Vs 41.89 mm in nonsurgical patients (P<0.001). Transsphenoidal approach was used in all patients (endoscope visualisation in 13/52). 12 months after the surgery, 50% had no tumour image on MRI. Some hormone deficiency was detected in 90.4% (38.5% of whom had panhypopituitarism) and the visual field deficits improved in 30%. Nine out of 52 patients required a second surgery and 11/52 received radiotherapy due to residual mass.

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Conclusion
Considering tumour size results they are similar to those reported in the literature but with a higher risk of hypopituitarism.

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EP754
Optic neuropathy following radiotherapy for Cushing’s disease followed by the diagnosis of pituitary carcinoma
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Introduction
ACTH-secreting pituitary carcinomas are rare neoplasms but there are not factors till now to predict their aggressive evolution nor a standard practice to their management.

Case report
We report a 43-year-old female patient presented in 1990 with Cushing’s syndrome due to ACTH-secreting pituitary microadenoma who had been submitted on trans-sphenoidal surgery with cure as defined by post-operative cortisol serum levels < 50 nmol/l. In 2008 she represented with clinical, biochemical and imaging recurrence, hence, 10 years after her first remission. She had repeat surgery similarly with cure as defined by post-operative cortisol serum levels <50 nmol/l but again a recurrence within 2 years. Since, no tumour was documented in imaging studies, she received external beam irradiation (in total a dose as high as 54 Gy) in 2005. However, her hypercortisolaemia was still uncontrolled and she was submitted in bilateral adrenalectomy. Ten months after radiotherapy, the patient was presented with declining visual acuity, and radiation-induced optic neuropathy (RON) was diagnosed. Despite treatment with glucocorticoids and hyperbaric oxygen, her vision did not improve. Two years later she was hypoglycemic with increased ACTH plasma levels. The ACTH plasma levels continued to increase reaching very high levels and in 2010 FDG-PET and conventional imaging confirmed the diagnosis of pituitary carcinoma with multiple liver metastasis and local disease. Since today we are trying to control, her disease with several recent chemotherapeutic and biological agents (cispitant + etoposide and temorolarmide + bevacizumab).

Conclusions
This case implies that the appearance of pituitary carcinoma cannot be excluded by the cure post trans-sphenoidal surgery nor can be prevented by a high dose of irradiation even this is so high to cause RON.

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EP755
Mortality of patients with non-functioning pituitary macroadenoma is significantly elevated: systematic analysis of 546 cases in a tertiary referral centre in the UK
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Introduction
Data on the mortality of patients with non-functioning pituitary macroadenoma (NFA) are very limited.

Aim
To assess the mortality of patients with NFA and factors predicting it.

Patients and methods
All patients presenting to our department with NFA between 1963 and 2011 were studied.

Status was recorded as either dead or alive, as of 31st December 2011.

Results
546 patients (333 males) were identified (median age at surgery 58.7 years; range 16.1–94.2). Data on mortality were available for all patients covering a median period of 8 years (range 1 month–48.5 years); 83 patients died (median age 77.8 years; range 36.4–98.3) (causes: cardio/cerebrovascular 32.5%, infections 30.1%, malignancies 28.9%, peri-infarction 1.2%, gastrointestinal hemorrhage 1.2%, suicide 1.2%, unknown 3.6%, and old age 1.2%). The SMR for the total group was 3.62 (95% CI: 2.90–4.47; P < 0.001), for those diagnosed before 1990 4.66 (95% CI: 2.65–7.63; P < 0.001) and for those after 1990 3.53 (95% CI: 2.77–4.44; P < 0.001). Clinical follow-up data (until date of death or date the database was frozen) were available for 436 patients (269 males, median age at surgery 58.5 years (range 16.11–94.19), 203/431 with no or intrasellar remnant – 228/431 with extrasellar remnant after surgery, median follow-up 6.9 years (range 1 month–48.5 years), 111/436 with regrowth of NFA, 188/436 received radiotherapy after primary surgery or for regrowth. Cox regression analysis (univariate approach) demonstrated that amongst age at surgery, NFA regrowth, radiotherapy, sex and extent of removal, the first three were significant predictors of mortality; after multivariate analysis using these three parameters, only age remained an independent significant factor (HR 1.097; 95% CI: 1.073–1.126; P < 0.001).

Conclusions
Despite the improvement in the last three decades, mortality of patients with NFA remains high. Apart from age, factors related with the management/outcome of the tumour including radiotherapy and recurrence are not independent predictors of mortality in this group of patients.

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EP756
Sheehan’s syndrome: a rare disease with typical symptoms
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Introduction
The enlarged pituitary gland of pregnancy is susceptible to any compromise to its blood supply. Sheehan’s syndrome (SS) occurs as a result of post-partum pituitary infarction or haemorrhage and usually leads to hypopituitarism. It can be fatal but clinical manifestations may change from one patient to another and symptoms may not occur for many years.

Methods
We analysed retrospectively five cases of women with SS aged 26–56 years, treated at Endocrinology Department between 2003 and 2014, to describe clinical manifestations. In the studied subjects the diagnosis of SS was made based on medical history, clinical symptoms, hormonal tests, and MRI scans.

Results
Mean age of the patients was 41.00 ± 12.33 years (range 26–56 years). All subjects had typical physical signs of SS. The duration between date of the last delivery and time of diagnosis was 9.82 ± 8.85 years (ranged from 1 month to 19 years). The number of pregnancies was from 1 to 4. We observed typical obstetric history of massive hemorrhage at delivery in three women, two of them received a blood transfusion. In two cases there was no overt obstetric complications. All patients lacked post-partum milk production and did not menstruate following delivery. According to the hormonal values, five analyzed women had total or partial secondary hypothyroidism, adrenal cortex failure and hypogonadotropic hypogonadism, prolactin, and GH deficiency. They used therapy such as: hydrocortisone (mean 25.00 ± 7.07 mg/day), levothyroxine (mean 75.00 ± 43.30 μg/day), and sex hormone replacement. Diabetes insipidus was found in one patient but it was transient. She was treated with desmopressin (120 μg/day) for 17 months. MRI scans revealed total or partially empty sella in three women and small (beyond the normal range) pituitary gland in two cases.

Conclusion
Although, SS is not a common disease, it should be remembered about concerning women with pituitary insufficiency developing at different times after delivery.

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EP757
Cure rates and survival in patients with acromegaly
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Introduction
An improvement of survival in patients with acromegaly was claimed in the last years, with multimodal new therapies.

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Implementation of clinical guidelines on the cancellation of dopamine agonists in the event of pregnancy in patients with hyperprolactinaemia tumour origin

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Aim
Clinical guidelines recommend the cancellation of dopamine agonists after confirmation of pregnancy as because further their use is unnecessary. However, an implementation of these recommendations in real clinical practice is unknown which became the aim of our present research.

Materials and methods
The study included 21 patients with prolactinomas who had 26 pregnancies ended in a single Neuroendocrinology Department between Jan 2001 and Dec 2013 were retrospectively studied by GH, IGFI levels at baseline and at final visit, therapy, pituitary failure, and date of the death. PAMCOMP computation program calculated standardized mortality ratio (SMR), Kaplan–Meier curve was used to compare the impact of different therapies on survival. Serum GH levels were measured by IRMA (sensitivity 0.1 ng/ml).

Results
35.02% patients obtained control of acromegaly: 17.3% were cured after neurosurgery and/or radiotherapy and additionally 17.6% were controlled by medication. Cure rate for surgery was 17.7% (35/197) and 15.03% (23/153) for radiotherapy. 49/128 (33.5%) patients treated by somatostatin receptor analogues (SSA), 8.3% (4/48) treated with dopamine agonist and 6/16 patients (37.5%) treated by GH receptor agonist were adequately controlled. All causes mortality ratio was similar with general population: SMR = 1.07 (95% CI 0.70–1.52), average follow-up of 2252.11 person-years (median 6.9 years). Females with last GH above 2 ng/ml had a high SMR = 2.51 (95% CI 1.37–4.22).

Operated patients with/without medication and/or radiotherapy had a better survival than untreated patients (rank log Mantel-Cox: P = 0.04 operated vs untreated patients, 0.05 operated + SSA patients vs untreated and 0.02 operated + irradiated vs untreated).

Conclusions
Patients with acromegaly and posttreatment GH level ≥2 ng/ml had a high mortality, especially women. Surgery treated patients, with additionally treatment for postoperative remnants, had a better survival, similar with general population.

Disclosure
This work received financial support through the project ‘CERO – Career profile: Disclosure for postoperatory remnants, had a better survival, similar with general population.

EP759

Alterations in thyroid hormone levels following GH replacement exert complex biological effects

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Introduction
Alterations in the hypothalamic–pituitary–thyroid axis have been reported following GH replacement, with a decline in circulating T4 concentration the most consistent finding. However, the clinical significance of GH-induced alterations in circulating levels of thyroid hormone is unclear.

Aim
To examine the relationship between changes in serum concentration of thyroid hormones and known biological markers of thyroid hormone action.

Methods
We performed a prospective study of 20 hypopituitary adult men before and after routine GH replacement. Serum TSH and thyroid hormone (free T4, total T4, free T3, total T3, and reverse T3) were measured before and after GH substitution. Changes in thyroid hormone concentrations were compared to alterations in serum biomarkers of thyroid hormone action. Resting energy expenditure (REE) and cardiac systolic time intervals were also evaluated as sensitive markers of thyroid hormone exposure.

Results
The mean daily dose of GH was 0.34 ± 0.11 mg. Following GH replacement, free T4 levels declined as expected (−1.28 ± 0.44 pmol/l; P = 0.02). Reverse T3 levels also fell (−3.44 ± 1.42; P = 0.03) and free T3 levels increased significantly (+ 0.54 ± 0.15; P = 0.03). REE did not rise as expected with GH substitution. SHBG and CK levels were unchanged. However, ferritin, copper, and caeruloplasmin declined suggesting reduced hepatic exposure to thyroid hormone (−26.8 ± 8.5; P = 0.005); (−1.7 ± 0.63; P = 0.02); and (−0.02 ± 0.01; P = 0.04).

Complex alterations in lipid profile, including a rise in large HDL particles (+1.75 ± 0.69; P = 0.02) were fall in intermediate density lipoprotein concentration were variably associated with changes in thyroid hormone and GH. Cardiac systolic time intervals were unchanged. Observed changes in thyroid hormone biomarkers were more pronounced in subjects with multiple pituitary hormone deficiencies.

Conclusion
Our study demonstrates that GH replacement does not improve the biological actions of thyroid hormone in adults.

Disclosure
This work was supported by an unrestricted educational grant from Merck Serono.

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EP760

Assessment of mean platelet volume in acromegaly and its relation with disease outcome

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Background
Acromegaly is associated with increased risk of coronary atherosclerosis and cardiovascular mortality. Changes in coagulation and fibrinolysis markers in acromegalic patients have been shown to indicate increase in the risk of developing cardiovascular disease. Mean platelet volume (MPV) is a marker of platelet functions and activity, and increased MPV is an independent risk factor of myocardial infarction and thrombotic events. In this study, we examined the levels of MPV in acromegalic patients before and after treatment compared to a control group.

Aims
To assess cure rates of different therapeutic protocols and the impact of these therapies on survival.

Methods
334 patients (224 F/110 M, mean age 48.1 ± 7.0 years) with acromegaly admitted in a single Neuroendocrinology Department between Jan 2001 and Dec 2013 were retrospectively studied by GH, IGFI levels at baseline and at final visit, therapy, pituitary failure, and date of the death. PAMCOMP computation program calculated standardized mortality ratio (SMR), Kaplan–Meier curve was used to compare the impact of different therapies on survival. Serum GH levels were measured by IRMA (sensitivity 0.1 ng/ml).

Results
35.02% patients obtained control of acromegaly: 17.3% were cured after neurosurgery and/or radiotherapy and additionally 17.6% were controlled by medication. Cure rate for surgery was 17.7% (35/197) and 15.03% (23/153) for radiotherapy. 49/128 (33.5%) patients treated by somatostatin receptor analogues (SSA), 8.3% (4/48) treated with dopamine agonist and 6/16 patients (37.5%) treated by GH receptor agonist were adequately controlled. All causes mortality ratio was similar with general population: SMR = 1.07 (95% CI 0.70–1.52), average follow-up of 2252.11 person-years (median 6.9 years). Females with last GH above 2 ng/ml had a high SMR = 2.51 (95% CI 1.37–4.22).

Operated patients with/without medication and/or radiotherapy had a better survival than untreated patients (rank log Mantel-Cox: P = 0.04 operated vs untreated patients, 0.05 operated + SSA patients vs untreated and 0.02 operated + irradiated vs untreated).

Conclusions
Our study show not ubiquitous implementation of clinical guidelines in the issue of cancellation of dopamine agonists at pregnancy confirmation with 54% patients continuing medications for more than 6 weeks of gestation.

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Methods
A total of 80 patients (24 were diabetic) treated in our clinic with the diagnosis of acromegaly between 2009 and 2014 and 65 (23 were diabetic) age- and gender-matched healthy controls were reviewed retrospectively. Demographic data of all subjects and postoperative cure and remission with medical management among acromegalic patients were recorded. Preoperative and postoperative MPV values as well as MPV values observed in patients with controlled disease on medical treatment were compared. In both groups bHbA1c levels and their relationship with MPV were also evaluated.

Findings
In this study, 47% of the acromegaly patients and 48% of the control subjects were females. The mean age both groups and the mean bHbA1c among diabetics in both groups were similar. MPV values were significantly higher in both the diabetic and non-diabetic acromegalic patients compared with the control subjects. Postoperative MPV values were significantly reduced compared to preoperative values in patients cured with surgery. Patients who achieved control with medical therapy after the failure of surgical intervention demonstrated MPV values similar to those reported in patients cured with surgery. When MPV values at presentation were evaluated in the acromegaly and control groups, it was shown that presence of diabetes mellitus, age and gender had no effect on MPV.

Conclusion
MPV can be considered as a marker for atherothrombotic process and prognosis of acromegalic patients.

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EP761
A rare case of papillary thyroid cancer: pituitary metastasis
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Introduction
Differentiated thyroid carcinoma (DTC) rarely represents with distant organ metastasis. Cerebral metastasis is seen in 0.4–1.2% of patients with distant organ metastasis. There are only 14 patients of DTC with pituitary metastasis reported in the literature. Here, we report a papillary thyroid carcinoma (PTC) patient represented with pituitary metastasis.

Case
A 68-year-old male patient has admitted to our hospital with a growing tumour on his anterior chest wall. On imaging there was a 5 cm mass on the manubrium sterni. The patient was referred to our clinic as the biopsy of the mass revealed PTC metastasis. During clinical evaluation there was 5 cm hypoechoc, hypervascular nodule on left thyroid lobe. Also, there were high fluorodeox-yglucose (FDG) affinity on pituitary region, thyroid left lobe, sternum, first lumber vertebrae and left humerus on positron emission tomography–computerized tomography (PET-CT) consistent with metastasis. Total thyroidectomy with lymph node dissection was performed and pathology revealed poorly differentiated insular type PTC. The pituitary lesion was also operated but could only be partially resected. The pituitary pathology showed PTC metastasis. The sternal mass could not be operated due to high morbidity and invasiveness. Radio-frequency ablation was performed but the mass was continued grow. After 3 months arterial embolisation was performed to the lesion. As the pituitary lesion was very close to the brain stem structures, radio-iodine treatment was decided to be contraindicated. 36 Gy conventional radiation therapy was given to the pituitary region. During all these treatment procedures sorafenib 400 mg/day was very close to the brain stem structures, radio-iodine treatment was decided to be performed to the lesion. When MPV values at presentation were evaluated in the acromegaly and control groups, it was shown that presence of diabetes mellitus, age and gender had no effect on MPV.

Conclusion
MPV can be considered as a marker for atherothrombotic process and prognosis of acromegalic patients.

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EP763
When the improbable happens: a case of acromegaly diagnosed during pregnancy
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Introduction
Pregnancy in a patient with acromegaly is uncommon, as the enlarging pituitary adenoma suppresses gonadotropin secretion rendering the patient amenorrhoeic and infertile. About 40% of the women with pituitary adenoma also have hyperprolactinaemia, which further decreases the likelihood of pregnancy.

Case report
A 32-year-old woman was sent to our centre in the first trimester of pregnancy with the diagnostic of gestational diabetes. Clinical examination revealed acromegalic features. Her blood pressure was normal. A few weeks before getting pregnant, because of a history of headaches and amenorrhoea, she underwent a brain magnetic resonance imaging (MRI) that showed a pituitary macroadenoma, with left cavernous sinus invasion but without compression of the optic chiasma. However, this result became available when she was already pregnant. Hormonal profile revealed elevated GH (80 ng/ml) and IGF1 (1442 ng/ml). Prolactin was also mildly elevated (38 ng/ml). She had no changes in visual acuity, visual fields, or fundus. She was medicated only with insulin for her diabetes, with excellent control. Serial visual field monitoring was performed, which remained normal, and signs and symptoms of acromegaly were stable. She delivered a full-term baby girl by caesarean section, healthy and without any malformations. Three months later, octreotide 20 mg once a month was started, with progressive decrease in GH and IGF1. After 6 months of treatment, a new MRI was performed showing a significant reduction of the tumour. She is now under octreotide 30 mg once a month and about 1 year after the beginning of somastostatin analogue the IGF1 level is 578 ng/ml, GH 3 ng/ml, and prolactin 19.7 ng/ml. Her acromegalic features had regressed.

Conclusion
Pregnancy in women with acromegaly can have a normal course, without obstetrical or foetal complications, and treatment can be postponed to the postpartum period.

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Endocrine Abstracts (2015) Vol 37

Background
Errors made with critical medicines such as desmopressin and hydrocortisone used in the treatment of endocrine conditions in hospitalised patients can undermine patient safety but are largely preventable.

Methods
Retrospective audit of adult patients admitted at the University Hospitals of Leicester NHS Trust between January 2013 and June 2014, prescribed desmopressin for cranial diabetes insipidus (CDI) or other medical conditions using electronic prescribing (ePMA). Safety concerns were recorded on a scoring system according to pre-defined parameters including patient confusion, abnormalities of serum sodium levels, evidence of missed or delayed administration of desmopressin and hydrocortisone.

Results
15 patients (seven males) with a median (IQR) age of 56 (17–85) years were identified. 31 hospital admissions were recorded with a median length of stay of 5 days (range 1–30). Among eight patients (17 hospital admissions) with CDI, history of confusion was observed in 12 admissions (70%), six admissions (35%) had abnormal admitting serum sodium levels, and 14 admissions (88%) had 39 missed/delayed doses of desmopressin. Common reasons included, medications unavailable (64.9%), no reason mentioned (15.8%), patient declined (7.0%) and nil orally or wrong timing of medication (12.3%). At least one dose of hydrocortisone was missed in 35.7% admissions. In the non-CDI cohort, seven patients had 14 admissions and in 64% admissions there were 18 missed/delayed doses of desmopressin. At least one safety concern was seen at every hospital admission in the CDI patient group.

Conclusion
Errors in critical medications such as desmopressin in prescribing and administration can affect patient safety and cause clinical harm. Increased pharmacovigilance and robust policies supporting medicines management of desmopressin in clinical areas are of paramount importance and will continue to be needed.
Pituitary adenoma in the elderly: a 10 years experience
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Background
Pituitary adenoma (PA) is an under-investigated pathology in the elderly.
Objective
To review our case records of patients >70 years with PA, in order to evaluate presentation symptoms, hormonal results, and pituitary morphology.

Patients
48 patients aged 70 years or older (21 females/27 males) were identified from the group of 610 patients with PA (7.9%) diagnosed at Neuroendocrine Unit, Clinic for Endocrinology, Belgrade, between 2005 and 2014. Median age in our group of elderly was 73 years (range 70–83).

Results
Thirty-six patients had nonfunctioning pituitary adenoma (NFPA), seven patients had acromegaly (ACRO), four patients had prolactinoma (PRL), and one patient had ACTH secreting PA. In majority of patients (n=44; 92%) macroadenoma was diagnosed (20–46 mm in diameter). Pituitary microadenoma was diagnosed in four patients (three ACRO and one NFPA). The commonest presenting symptoms were visual deterioration (n=23; 48%) and headache (n=22). Hypopituitarism (due to secondary hypocorticism) was diagnosed in eight patients (17%). In five patients (all with hyponatremia and hypocorticism) loss of memory, confusion, and depression (n=5), loss of memory, confusion, and depression (n=5). In four patients, the disease was incidentally discovered during CT or MRI for cerebral ischemic attacks. Endocrinological evaluation showed global anterior hypopituitarism in 18 patients (38%) and partial hypopituitarism in seven patients (15%; four patients had GH and gonadotropin deficiency and three patients had GH, gonadotropin, and TSH deficiency). Twenty-eight patients (58%; 24 NFPA, three ACRO, and one silent PRL) underwent transsphenoidal surgery, with no severe perioperative complications. Immunohistochemistry was performed in 12 patients (seven NFPA were positive for gonadotropins, one NFPA was GH sparsely granulated, and four NFPA patients were null cell PA). Ki-67 antigen expression was indicative of low proliferative activity.

Conclusion
In the last 10 years pituitary adenomas have been recognised more frequently in the elderly. Most were non-functioning pituitary macroadenomas which presented with visual deterioration and hypopituitarism. If hypopituitarism is diagnosed in the elderly with PA, then it can be a life-threatening condition.

EP766
The metabolic relevance of angioptcin-like protein 4 in different states of GH/IGF1 excess or deficiency
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Introduction
Somatostatin analogues (SSA) present the treatment of choice in patients with previously poorly controlled acromegaly.

Methods
We conducted a retrospective analysis of acromegalic patients enrolled in the Network of Excellence for Neuroendocrine Tumors Munich and treated with the SSA lanreotide.

Results
Fifty-six acromegalic patients (25 females; mean age 59 years; 33 with macroadenoma) switched to lanreotide from previous medical therapies for acromegaly (n = 33; 19 due to insufficient biochemical control, 14 due to poor treatment tolerability) (n = 11 switch from dopamine agonists, n = 15 switch from octreotide, n = 3 switch from pegvisomant, and n = 4 switch from combination therapy) or were medically treatment-naive (n = 23). Of the 56 patients, 29 patients started on 60 mg, 4 patients started on 90 mg, and 20 patients started on 120 mg lanreotide; three patients started on combination therapy with dopamine agonists or pegvisomant. Mean follow-up time on lanreotide were 4.6 ± 4.6 years. Lanreotide led to clinical improvement of acromegalic signs and symptoms in 96%. Mean GH concentration decreased from 10.5 ± 25.9 to 3.2 ± 4.9 ng/ml after 3–6 months (P < 0.017) and to 2.6 ± 3.2 ng/ml (P < 0.001) at the last evaluation on lanreotide (GH ≤ 2.5 ng/ml in 44 and GH ≤ 1.0 ng/ml in 37 patients). Mean IGF1 concentration decreased from 1.6 ± 1.0 to 1.1 ± 0.5 xULN after 3–6 months (P < 0.001) and to 0.8 ± 0.3 xULN (P < 0.001) at the last evaluation on lanreotide. Acromegaly was biochemically controlled in 20 and 73% of patients at baseline and at the last evaluation on lanreotide respectively. Additionally, lanreotide had significant favorable impact on patients’ glycemic status, leading to significant decrease of fasting plasma glucose after 3–6 months of treatment (157.4 ± 141 mg/dl vs 106.9 ± 20.9 mg/dl; P < 0.001). Lanreotide was well tolerated with the exception of transient mild gastrointestinal discomfort in 21%.

Conclusion
The SSA lanreotide alone or in combination is safe, effective and well-tolerable in the treatment of previously poorly controlled acromegaly.

Disclosure
This work was supported by an independent research grant from IPSEN.

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EP767
Response to pasireotide in an acromegalic patient with resistance to conventional medical treatment
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Introduction
Surgery is the primary therapy in most acromegalic patients. When persistent disease is observed, adjuvant medical therapy is used. Pasireotide is a somatostatin analogue (SSA) not approved for acromegaly therapy yet, but with a potentially better response, given that it binds to four out of five somatostatin receptors.

Materials and methods
We present the case of an acromegalic patient with resistance to many therapies and response to treatment with pasireotide.

Clinical case
A woman diagnosed in 1993, at the age of 24 years, of GH-producing pituitary macroadenoma (3.3 × 2.5 cm). She underwent surgery twice, with only partial resection, followed by radiotherapy and medical treatment. She was on s.c. octreotide, with partial response. Later on, bromocriptine was added with no improvement in GH/IGF1 levels. MRI showed empty sella at 1996. In 2001 medical therapy was switched to a dose of 30 mg of octreotide LAR/4 weeks plus a maximum tolerated dose of cabergoline (2 mg/week), without normalisation of IGF1 levels. In 2008 pegvisomant (15 mg s.c. daily) was used, achieving normal levels of IGF1, but causing headache and lipohypertrophy. On 3 days/week administration (120 mg/week), elevation in IGF1 level and persisting lipohypertrophy were observed. We requested compassionate-use treatment with pasireotide 40 mg/4 weeks. First dose on June 6th 2012 and increased to 60 on 2013.

01/06/2012 01/09/2012 29/08/2014
GH (ng/ml) 33.9 8.0 2.3
IGF1 (101–267 ng/ml) 661 709 261

In November 2013 a basal glucose value of 145 mg/dl and HbA1c 6.7% were observed. Mefenorm and later on vildagliptin were indicated and glucose control was achieved.

Conclusion
Pasireotide has got a clinical improvement and IGF1 control in this patient. Diabetes is under control on dual therapy.

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EP768
Exogenous administration of GH increases linear growth velocity at higher doses during pre- and early puberty in GH deficient short stature children
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In GH deficiency (GHD), which is a medical condition caused by problems in the pituitary gland, the body does not produce sufficient amount of GH, resulting in short stature in children. The treatment of GHD short children with exogenous GH increases linear growth velocity (LGV). The present study determined the effect of exogenous GH treatment on LGV in GH deficient short stature children.

Different ages (5–18 years) and stages (pre-, early, mid, and late) of pubertal development. GH replacement therapy caused greater increases in LGV at higher doses at pre- and early puberty in both female and male patients as compared to GH treatment at mid and late puberty. The plasma concentrations of GH and IGF1 increased significantly in all patients as compared to those found prior to GH treatment, which indicates that increases in LGV is secondary to augmentation in IGF1 secretion. In conclusion, the present study demonstrates that patients of GHD grow at a greater rate at higher doses of GH. The current investigation also shows that GH therapy caused higher increases in LGV at pre- and early puberty in both girls and boys through its effects on IGF1.

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EP769
Evolution of metabolic and psychiatric disorders after remission of Cushing’s disease
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Introduction
Cushing’s disease (CD) is a rare endocrine disorder characterized by endogenous hypercortisolism, which is associated with metabolic and psychiatric disorders. It is essential to understand the impact of normalization of serum cortisol in the evolution of these comorbidities.

Aims
To evaluate the evolution of metabolic and psychiatric disorders after biochemical control of hypercortisolism in patients with CD.

Methods
Retrospective observational study of patients with CD who underwent pituitary surgery between January 1998 and October 2013. Clinical data were evaluated at diagnosis and at the last evaluation of hospital consultation. Remission was defined as normal urinary free cortisol and normal plasma cortisol after overnight or low-dose dexamethasone suppression test.

Results
Forty-five patients were included: 87% (n = 39) females, mean age 32.8 (12.9) years and mean follow-up period 90.4 (56.7) months. After pituitary surgery, remission of CD was observed in 73.3% (n = 33). Recurrence of CD was detected in 30.3% (n = 10) of those patients after a mean of 64.4 (36.0) months after the first intervention. At diagnosis, 65.8% were hypertensive, 31.7% diabetic, 41.5% had dyslipidemia, and 46.5% psychiatric disorders. Of the 41 patients in remission at the last evaluation: 29.1% were under the same number of antihypertensive drugs, 20.8% discontinued them, 20.8% reduced their number, 16.7% remained without medication, and 12.5% increased; remission of diabetes occurred in 15.3% of patients and 80% of those who initially were on insulin suspended it; the anti-dyslipidaemic therapy was discontinued in 11.8% and psychotropic drugs were stopped in 55.5%. The mean initial BMI was 32 kg/m² and no significant differences regarding BMI were found after biochemical control of hypercortisolism. However, 46% of patients had a reduction in BMI class.

Conclusion
Biochemical control of hypercortisolism seems to improve the associated metabolic and psychiatric disorders in CD. However, as it is not possible to predict the evolution of these comorbidities it is mandatory an appropriate follow-up, evaluation and treatment of these patients.

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EP770
Sex-related differences in clinical presentation and outcomes of Cushing’s disease: a study from a referral centre
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In GH deficiency (GHD), which is a medical condition caused by problems in the pituitary gland, the body does not produce sufficient amount of GH, resulting in short stature in children. The treatment of GHD short children with exogenous GH increases linear growth velocity (LGV). The present study determined the effect of exogenous GH treatment on LGV in GH deficient short stature children.

Different ages (5–18 years) and stages (pre-, early, mid, and late) of pubertal development. GH replacement therapy caused greater increases in LGV at higher doses at pre- and early puberty in both female and male patients as compared to GH treatment at mid and late puberty. The plasma concentrations of GH and IGF1 increased significantly in all patients as compared to those found prior to GH treatment, which indicates that increases in LGV is secondary to augmentation in IGF1 secretion. In conclusion, the present study demonstrates that patients of GHD grow at a greater rate at higher doses of GH. The current investigation also shows that GH therapy caused higher increases in LGV at pre- and early puberty in both girls and boys through its effects on IGF1.

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Introduction
Cushing’s disease (CD) presents a marked female preponderance, with a female-to-male ratio of 3–8:1, but whether this skewed gender distribution has any relevance to the presentation and outcomes of CD is not well understood.

Aim
To evaluate sex-related differences in the presentation of CD, as regards: biochemical indices of hypercortisolism; complications of disease and outcomes.

Methods
Observational, retrospective study of patients with CD confirmed on pituitary surgery between January 1998 and October 2013.

Results
We included 45 patients, of whom 39 (87%) were women. The mean age at diagnosis was 38.2 (12.9) years and the mean follow-up period was 90.4 (56.7) months. Diabetes was more prevalent in males (50% vs 26.3%), as well as hypertension (83% vs 61%) and dyslipidaemia (66.7% vs 40.5%). The psychiatric disorders were more frequent in females (56.8% vs 16.7%). Most women (56.8%) presented a microadenoma on MRI, 33% of men had a macroadenoma and 50% a macroadrenoma. CD remission was found in 74.4% of women who underwent pituitary surgery; in men remission occurred in 66.7%. At diagnosis, there were no significant differences in serum cortisol levels, urinary free cortisol, midnight cortisol or cortisol levels after overnight dexamethasone suppression test. Male patients had higher basal levels of ACTH (106.5 (46.0) pg/ml vs 70.5 (38.7) pg/ml, P = 0.048) and serum cortisol after 2-day dexamethasone suppression test (40.5 (51.7) μg/dl vs 13.3 (11.0) μg/dl, P = 0.015). No differences were found in serum prolactin or urinary free cortisol suppression after high-dose suppression test, by sex.

Conclusion
Biochemical indices of hypercortisolism, metabolic and psychiatric disorders, as long as outcomes of CD differed by sex. Understanding this dimorphic pattern may be relevant in order to define the adequate diagnostic work-up and follow-up of these patients.

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EP771
Association of hormonal changes with disease severity and mortality rate in critically ill patients
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Introduction
Endocrinological and metabolic changes can occur in critically ill patients, which may affect the prognosis and outcome. The hypothalamic–anterior–pituitary axis (HPA) plays a crucial role in the endocrine regulation of metabolic and immunological homeostasis. In this prospective study, we evaluated the pituitary–adrenal–gonadal–thyroid axis in the adult Intensive Care Unit (ICU) patients, their outcome, the association between these hormonal changes and ‘The Acute Physiology and Chronic Health Evaluation II score (APACHE II)’, Sequential Organ Failure Assessment (SOFA), length of hospitalisation and mortality.

Methods
Patients hospitalised in adult ICU (not for trauma or operation) between January 2014 and January 2015 were enrolled in this study. Severity of illness was assessed by APACHE II and SOFA on admission to the ICU and 15 days later. Blood samples were collected within the first 4 h of ICU admission and 15 days later for measurement of anterior pituitary and end organ hormones.

Results
Total patient number was 157. Eighty-five patients were in survival (S), 72 patients were in the non-survival (NS) group. In the NS group, patients’ mean age, APACHE II and SOFA scores at the admission were significantly higher. In the NS group median GH, E2, and cortisol levels were significantly higher whereas median FSH, LH, ITSH, and IT4 were lower. Fifteen days after admission, there was significant increase in median IGF1 and ACTH levels and decrease in median cortisol and SOFA scores compared to baseline values. Strongest predictors for mortality were found to be hospitalization length, SOFA score, deltaTSH, and age. None of the other endocrine parameters had an effect on mortality.

Conclusion
In critical illness, activation of the HPA and the cortisol response are essential for survival. Combinations of endocrine parameters may provide better indices than measurement of a single hormone or an APACHE II-based score.

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EP772
Indirect immunofluorescence for detection of pituitary antibodies
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Introduction
Definitive diagnosis of lymphocytic hypophysitis (LH) lacks a pathological analysis. The detection of pituitary antibodies (PAB) with the current methods presents variable results and its clinical utility is therefore limited. Recently, new methods were released for the interpretation of indirect immunofluorescence (IIF), which can increase the specificity for detection of PAB.

Methods
We evaluated four patients followed in endocrinology consultation with clinical suspicion of LH (patient 1: 49 years old female with pan-hypopituitarism beginning 40 days after delivery and an empty sella on MRI; patient 2: 20 years old male with isolated ACTH deficiency and gynecomastia; patient 3: 59 years old female with previous complaints of severe headache and dysesthesia starting at 42 years, MRI showing pituitary enlaergment with diffuse enhancement after contrast and pan-hypopituitarism ever since; patient 4: 39 years old male with hypogonadotrophic hypogonadism and autoimmune thyroiditis) and one patient with definitive diagnosis of LH; and patient 5: 27 years old female, with severe headaches beginning 1 week before delivery, MRI compatible with a pituitary macroadenoma with diffuse enhancement after contrast. Detection of PAB by IIF was carried out in a specialised centre. The presence of PAB was considered positive whenever a granular of diffuse cytosolic pattern were present, after using purified IgG and Fc blockade, if necessary.

Results
We obtained positive results in 40% of samples (two out of five). Patient 1: negative; patient 2: mild perinuclear positivity (1+); patient 3: negative; patient 4: cytosolic positivity, granular pattern; and patient 5: cytosolic positivity, diffuse pattern.

Discussion and conclusions
The patient with histological diagnosis of LH exhibits a diffuse cytoplasmic pattern, as usually happens in pituitary disease of autoimmune etiology. The granular cytosolic pattern of patient 4, which is strongly suggestive of autoimmune, might establish diagnosis of LH. Detection of PAB by IIF, according to the immunostaining patterns, can help in the classification and management of these patients.

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EP773
Clinical characterisation of acromegaloïdism in a controlled prospective study
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Acromegaloïdisms are usually reported as isolated cases that are not well characterised clinically. Indeed, most such cases were reported several decades ago, part of the reason why our knowledge about this entity is scarce. By contrast, clinical situations suggestive of acromegaly are not so infrequent, in which basal GH and IGF1 levels lie within a normal range, the GH responses to OGTT
EP774
Can use of the European diagnostic pathway improve diagnosis and management of hyponatraemia in a District General Hospital? An audit cycle
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Introduction
Despite the commonality of hyponatraemia in everyday clinical medicine it is often a poorly managed condition in acute medical patients. A European guideline for diagnosis and management was published in 2014 to address such problems.
Aims
To assess the standard of management of patients with hyponatraemia admitted to the medical departments in a rural District General Hospital. To improve investigation, diagnosis, and management of these patients where necessary.
Methods
A review of medical notes and biochemical tests was carried out for 69 patients admitted to the medical assessment unit with serum sodium below 130 mmol/l over a 3-month period. Adoption of the European guideline diagnostic pathway, creation of an investigation set’ and educating junior doctors and nurses were used as tools to improve management. Emphasis was placed on use of urine osmolality and sodium as tools to improve management. Subsequent re-review of management after change was carried out for 79 patients over a similar timeframe.
Results
Before change: only 13% of euvolaemic patients had a urine osmolality and sodium performed, only 25% of patients had causative medications stopped and only 45% of all patients had a cause established. After change: 51% of euvolaemic patients had a urine osmolality and sodium performed, 66% of causative medications stopped, and 73% of all patients had a cause established. In patients who had a urine osmolality and sodium performed a 90% diagnostic pick-up rate was found, compared to just 63% in those who didn’t.
Conclusions
Investigation and management is often neglected in acute medical patients. Using guidelines, education and support tools for doctors and nurses improvements can be made in both investigation and management of these patients. Our findings support European guidance on use of urine osmolality and sodium early in the diagnostic process.
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EP775
Congenital pituitary stalk interruption syndrome with isolated GH and TSH deficiency and Rathke’s cleft cyst: an incidental association
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Introduction
Congenital pituitary stalk interruption syndrome (PSIS) is a rare condition, characterized by the triad (not always complete): absence/hypoplasia of the pituitary stalk, hypoplasia/aplasia of the anterior pituitary and absence or ectopy of the posterior pituitary high signal intensity, on magnetic resonance imaging (MRI). PSIS implies a permanent GH deficiency, in 77% associated with other pituitary hormones deficiencies. The aetiology remains uncertain, but some genes have been implied. Rathke’s cleft cysts (RCC) present typically as intrasellar and/or suprasellar benign lesions, the most common incidentally discovered sellar lesions (few mm to 2 cm diameter), with a female:male ratio of 1:3.
Case report
A 18-year-old boy was referred from the Pediatric Endocrinology Department, with GH deficiency and central hypothyroidism (CH) diagnosed at the age of 9. Recombinant GH therapy had already been suspended (after 9 years; target height 170 cm achieved) and he was only on levothyroxine. MRI at 8 years of age had revealed a small pituitary gland, absence of the high signal intensity in the posterior pituitary, pituitary stalk atrophy, and a small pineal cyst. Reevaluation showed no other pituitary hormone deficiencies. There were no symptoms of diabetes insipidus. Follow up MRI (23 years old) showed a 7 mm sellar and suprasellar cystic lesion, suggestive of RCC, causing pituitary compression, posterior pituitary hypoplasia, and absence of posterior pituitary bright spot in T1. Until now, 1 year later, his clinical condition remains stable.
Conclusions
In this clinical case, a patient with PSIS had a RCC incidentally diagnosed in a follow up MRI. Paediatric cases have been reported but rarely, as RCCs grow slowly, becoming clinically evident later in life. Symptoms are uncommon and associated with mass effects. As there is compression of the pituitary gland, closed follow-up must be kept. Genetic tests results are pending.
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EP776
High diversity of Cushing’s disease in patients with corticotrophic macroadenoma
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Introduction
In 7–20% of cases, Cushing’s disease is due to ACTH-producing macroadenoma. Aim of the study was to present our observations concerning endoscopic, clinical, and therapeutic diversity of Cushing’s disease in patients with macrocorticotropinomas.
Material and methods
Retrospective analysis of medical records of nine patients (5F; 4M) hospitalized in 2002–2015.
Results
Four of the patients (2F; 2M) were diagnosed before they were 40 years old (mean age 28.5) and five (3F; 2M), >40 (mean age 50). In 3F tumour was initially discovered as microadenoma. A woman (23) first underwent bilateral adrenalectomy because of inability to neurosurgery and 5 years later Nelson’s syndrome developed. In two consecutive females (49 and 52) at the moment of diagnosis MRI revealed microadenomas 9×7 and 5×4 mm respectively. In the first female 2 years after initial neurosurgery consecutive four transphenoidal reoperations, stereotactic radiotherapy, and bilateral adrenalectomy were conducted. Then she developed Nelson’s syndrome. Propranol a consecutive rapid tumour’s invasion, thymolzolamide and bevacizumab were introduced. She died 7 years after the diagnosis. In the second patient tumour regrowth was observed 6 years after the first neurosurgery and because of failure of second adrenalectomy and mild hypercortisolism she was qualified to pasireotide therapy. In six patients (2F; 4M) the pituitary tumours were initially diagnosed as macroadenomas. One patient with 5 cm tumour and overt hypercortisolism died after craniotomy. Another patient presented cyclic Cushing’s syndrome with pituitary macroadenoma discovered after 7 years’ observation. In the next patient unique cause of Cushing’s disease was Crooke’s macroadenoma, refractory to two neurosurgeries with good response to themozolamide. In two cases (1F; 1M) macrocorticotropinomas were discovered as incidentalomas and operated as clinically inactive (silent) tumours. In these patients the tumour recurred 5 years after the first neurosurgery and visible hypercortisolism developed.
Conclusion
Macrocorticotropinomas are very heterogenic group of pituitary tumours with high aetologic, clinical and therapeutic diversity.
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EP777
Changes of prolactinomas during pregnancy and lactation

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Aim
To assess the size changers of prolactinomas after pregnancy and lactation.

Material and methods
We have analyzed the Russian register of tumors of the hypothalamic–pituitary region and conducted additional surveys of patients with prolactinomas who had pregnancy. We obtained data from 33 patients with prolactinomas who had 45 pregnancies and MRI studies prior and during/after pregnancy and lactation. Five patients had macroadenomas and 40 microadenomas.

Results
In 55.6% (25/45) of prolactinomas did not change after the pregnancy (including in three patients with macroadenomas). In 20% (9/45) they increased in size, including two macroadenomas. Growth of pituitary adenomas in two cases was accompanied by clinical symptomatology (visual field loss and complete loss of vision in one eye). 22.2% (10/45) of patients experienced the decrease in size of prolactinomas, which was observed only with microadenomas, and in three cases complete involution was noted. Information on lactation period and MRI evaluation was available for 34 pregnancies in patients with prolactinomas. According to the recommendations of doctors lactation was stopped immediately after birth with the help of dopamine agonists in 23.5% (8/34) of cases. In 87.5% (7/8) of these patients MRI did not show any changes from baseline and in one patient (12.5%) microadenoma had increased in size to macroadenoma without clinical significance. 26/34 patients nursed their children on average of 12 (2.8) months and often stopped lactation due to doctor’s recommendations with the help of dopamine agonists. In these patients according to MRI no changes were found in the pituitary adenoma size in 50.0% (13/26) cases, adenoma decreased in 26.9% (7/26), and increased in 23.1% (6/26). The patients with the increased size of prolactinoma during lactation had the shortest duration of lactation – 5 (2.3) months.

Conclusion
While the majority of pregnancies and lactation in patients with prolactinomas is not associated with adverse complications from the adenoma site, there is still a substantial risk in one in five women to experience tumor growth, though mostly subclinical, which raises the need of better prediction of such unfavorable outcomes.

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EP778
Pituitoma: a rare tumour

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Introduction
Pituitoma is a low-grade glioma of the suprasellar and sellar regions that is rarely described (about 60 cases in the literature). The clinical, laboratory, and neuroradiological findings are not pathognomonic, and therefore definitive diagnosis is only possible after surgery and histopathological study. Total resection is the treatment of choice, since subtotal removal can often lead to recurrence or progression.

Case report
We report the case of a Caucasian male with no significant medical history who develops isolated frontal headache at the age of 48. Magnetic resonance imaging (MRI) revealed an expansive sellar and suprasellar lesion, with 14 mm, well-defined limits, bright homogeneous enhancement with gadolinium, associated with a slight deviation of the optic chiasm. Hormonal study was normal. The patient continued to be followed in Neurosurgery consultation and after 4 years presented complaints of gradually worsening visual disturbances, progressively decreased libido and erectile dysfunction. On visual field testing, a bitemporal hemianopia was noted. MRI revealed millimetric increase of the tumour. He underwent transnasal/transphenoidal surgery, which resulted in a partial removal due to difficulty in controlling bleeding. The histopathological examination showed a tumor composed of bipolar cells, with immunohistochemical positivity for vimentin and S100 protein, Ki-67 <2% – pituitoma. The postoperative hormone study revealed panhypopituitarism. The control MRI detected significant residual tumour, so it was decided to propose the patient for radiosurgery treatment.

Conclusions
This pituitoma case illustrates a diagnosis that, although rare, should not be excluded from the possibilities available before a suprasellar or sellar lesion that presents with certain cardinal radiological features. The persistence of significant residual tumour was due to the bleeding tendency of the lesion during surgery. Awareness of the possibility of pituitoma before surgery would be ideal for appropriate treatment planning, with possible preoperative embolisation of the tumour.

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EP779
The impact of surgical management of Cushing’s disease in pregnancy on foetal outcomes

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Background
Cushing’s disease is a condition rarely encountered during pregnancy. It is known that hypercortisolism is associated with increased maternal and foetal morbidity and mortality.

Aims and methods
A comprehensive search of the literature was performed for cases of Cushing’s disease in pregnancy including our own case. Analysis was performed of all pregnant patients with Cushing’s disease who were treated with surgery compared to a surrogate control group of pregnant patients with untreated Cushing’s syndrome. Foetal outcomes were compared including preterm labour, intrauterine growth retardation, intrauterine foetal death, and neonatal death. Cases of Cushing’s disease who were not in remission or with missing post-operative data were mentioned but excluded from our statistical analysis.

Results
There were 11 previously reported cases of Cushing’s disease surgically managed between the 10th and 23rd weeks of pregnancy. Of those, three cases were excluded due to lack of post-operative biochemical results or follow-up information and one case was excluded due to lack of biochemcial remission. Foetal complications occurred as follows: preterm labour 29% (2/7), intrauterine growth retardation 29% (2/7), neonatal death 14% (1/7), and intrauterine foetal death 9% (0/7). Of these, there was a significant reduction (P =0.04) in preterm labour when compared to the preterm labour rates occurring in untreated Cushing’s syndrome. Other foetal complications were not statistically different. Out of the 11 case reports, maternal and surgical complications included pre-eclampsia (n = 4), syndrome of inappropriate antidiuretic hormone (n = 2), diabetes insipidus (n = 1), cerebrospinal fluid leak (n = 1). Three patients did not have any maternal or surgical complications.

Conclusions
Transphenoidal surgery for Cushing’s disease can be performed safely during the second trimester of pregnancy. The rate of preterm labour is significantly lowered when Cushing’s disease is surgically treated and biochemical remission is achieved during pregnancy.

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EP780
Neutrophil/lymphocytes ratio in patients who have hypogonadotropic hypogonadism

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Neutrophil/lymphocytes ratio in patients who have hypogonadotropic hypogonadism.

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Introduction
The effects of sex steroids on lymphocytes count and functions are well known and it is propounded that autoimmune diseases more common in women. NLO index is an indicator of inflammatory situation. In this study, it has been aimed that neutrophil/lymphocytes ratio (NLO) calculation by determining neutrophil/lymphocytes values in patients who diagnosed as hypopituitary pituitary hypogonadism and searching that whether there is significant difference between healthy group or not.

Method
33 patients who have been diagnosed as hypopituitary hypogonadism, 56 people who have no statistically significant difference in point of age, BMI among them and they are completely healthy people as a control group, totally 89 people have been incorporated to the study. It has been calculated that patient group’s age average is 22.4±7.4 and control group’s age average is 23.1±6.4. Statistically significant difference couldn’t be determined among them (P=0.6). Patients’ neutrophil and lymphocytes values have been evaluated by studying. Patients’ C-reactive protein (CRP) and testosterone levels have been registered again by studying.

Results
In the study results, patient group NLO has been founded as 1.8±1.3 and healthy group NLO has been founded as 1.4±0.3 and statistically significant difference has been determined among them (P=0.03). Statistically significant difference has been respectively determined between patient group and healthy group in point of white blood cell count (7.9±3.1 and 6.7±1.1, P=0.04), neutrophil (4.6±2.7 vs. 3.7±0.7, P=0.03), lymphocytes (2.4±0.6 and 2.7±0.7, P=0.04) and CRP (2.0±1.3 and 0.9±1.0, P=0.01). In the group which has hypopituitary hypogonadism; while positive correlation is being determined between NLO (r=0.228, P=0.03), white blood cell (r=0.564, P<0.0001) and neutrophil (r=0.847, P<0.0001), negative correlation has been determined between testosterone and lymphocytes count (r=-0.0395, P=0.0001).

Discussion
We can say that sex steroids can be effective on lymphocytes and neutrophil count depending on the results from this study. Whether to return to normal of sex steroids replacement with these functions must be demonstrated by more detailed studies.

Conclusion
This is the first study of CO-GHD in an Irish cohort. The results are consistent with international literature. In addition, family history of CO-GHD may be a predictor for persistent GHD. We anticipate that >60% of our cohort will have persistent GHD at the time of transition warranting continuation of GH.

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EP782
Some clinical characteristics and cardiovascular risk of our patients with hypopituitarism during long-time follow-up
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Several studies have pointed to increased morbidity and mortality in patients with hypopituitarism, particularly from cardiovascular diseases, regardless of the application of the substitution therapy. The aim of this study was to present clinical characteristics and cardiovascular risk of our patients with hypopituitarism during 20 years of follow-up.

Methods
Sixty patients with hypopituitarism without patients with acromegaly and Cushing disease were analysed retrospectively/prospectively. The investigated group consisted of 32 men and 28 women, of the age average of 52.18±17.51.

Results
Mean BMI values were 27.78±6.53 kg/m². The average age of the examinees at the time of diagnosis was 40.20±18.69. The most common causes of hypopituitarism were pituitary macroadenomas (53.33%) and craniopharyngeoma (21.66%). Partial hypopituitarism with lesion of two and more functions was present in 64.41%, panhypopituitarism in 28.81%, and 6.78% had an isolated deficiency of one adrenocortical hormone. Patients were treated with substitution therapy: L-thyroxine, hydrocortisone, growth hormone, sexual steroids, while diabetes insipidus was treated with desmopressin. 6.66% of subjects treated with dietary nutrition regime had diabetes mellitus type II. The therapy of hypopituitarism was followed by insignificant reduction in systolic and diastolic blood pressure. Elevated values of total cholesterol over the course of therapy significantly decreased (P≤0.009) as well as values of LDL cholesterol (P≤0.005). The values of HDL cholesterol and triglycerides were not significantly changed during treatment. Cardiovascular incidents were recorded in only 11.66% of the subjects, and a lethal outcome in one patient due to sepsis.

Conclusion
The results indicate that the middle aged people are most prone to the risk developing hypopituitarism, mostly due to a tumor in the sellar region and its treatment. Cardiovascular risk factors are present in untreated hypopituitarism. Despite substitution therapy, the oftenness of cardiovascular incidents is present. DOI: 10.1530/endoabs.37.EP782

EP783
Long-term recurrence in nonfunctional pituitary adenomas after surgery
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Object
Nonfunctioning pituitary adenomas can experiment recurrence and/or progression (R/P) several years after surgery in about 15–50% of patients. There is few evidence about risk factors that could predict R/P. The aim of this study is to identify them and describe our experience through a long term of follow-up in pituitary macroadenomas.

Methods
Retrospective cohort analysis of 64 patients who underwent surgery between 1990 and 2013. The main outcome was to evaluate prevalence of R/P during the follow-up, based on imaging criteria and identify some risk factors for R/P.

Conclusion
This is the first study of CO-GHD in an Irish cohort. The results are consistent with international literature. In addition, family history of CO-GHD may be a predictor for persistent GHD. We anticipate that >60% of our cohort will have persistent GHD at the time of transition warranting continuation of GH.

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Results
Over a median follow-up of 10.12 years, there was 46% of R/P after surgery at a median time of 4.6 years, the cumulative risk of being free of R/P was 62% by 5 years and decrease to 45% by 15 years after surgery. Multivariate cox proportional hazard regression analysis identified the following risk factors as associated with increased risk of recurrence: radiotherapy after surgery (hazard ratio 2.90, 95% CI 1.15–7.46, P = 0.023) and the tumour size at diagnosis (hazard ratio 1.05 CI 1.009–1.10, P = 0.019).

Conclusions
Patients with NFPA need long-term follow-up because they have a high risk of R/P over time. Radiotherapy after surgery decreases the risk of recurrence or progression specially after five years. The tumour size at diagnosis is an independently risk of R/P.

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EP784
Recurrent of GH-secreting pituitary adenomas during puberty in children with germline AIP mutations: a clinical challenge
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Germline AIP mutations (AIPmut) predispose to young onset somatotroph pituitary adenomas (GHPA) and gigantism. AIPmut GHPA are often aggressive and resistant to pharmacological treatment, which may be especially challenging in the paediatric setting. We report our experience with two young Italian AIPmut male patients with incipient gigantism due to childhood pituitary macroadenomas, who both experienced recurrent GH/IGF1 hypersecretion followed by tumour regrowth during puberty.

Case 1
Patient A developed incipient gigantism due to a familial R304X AIPmut. He was successfully operated on at the age of 9 years, for an intrasellar macroadenoma (12 mm). Two years later, spontaneous puberty occurred and IGF1 increased progressively. Final diagnosis of disease recurrence was made at the age of 14.5 years and pharmacological treatment with cabergoline (CAB) and somatostatin analogues (SSA) was started with a partial response.

Case 2
Patient B complained of visual defects at the age of 11.5 years, in a sporadic setting of accelerated growth. MRI showed a pituitary macroadenoma with suprasellar extension (27 mm), which was successfully operated on. Plasma GH/IGF1/PRl and growth velocity normalized. A germline A277P AIPmut was found. Soon afterwards spontaneous puberty occurred and IGF1 increased progressively. Two years later he was started on CAb due to modest biochemical/clinical worsening and initial tumour regrowth. Thereafter, an increasingly aggressive tumour recurrence developed, requiring multiple treatment modalities with SSA, CAB and/or preganvisom. He was re-operated at the ages of 14 and 18 years. and then underwent radiotherapy. Medical therapy was progressively withdrawn, with no need for hormone replacement therapy currently.

Comments
Both patients completed puberty, with heights stabilising at 191 and 190 cm, respectively. Early diagnosis of disease recurrence is of special importance in patients with incipient gigantism, but this may be very challenging during puberty in the absence of radiological evidence of tumour regrowth.

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EP785
Interpretation of dynamic test results in secondary hypocortisolism post pituitary surgery and hydrocortisone replacement doses
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Background
Following pituitary surgery, dynamic testing with insulin tolerance (ITT) or glucagon stimulation testing (GST) is used to identify patients with secondary hypocortisolism who require glucocorticoids. High glucocorticoid replacement doses are associated with adverse effects, and the optimal replacement dose is unknown.

Aim
We aimed to assess the interpretation of dynamic testing post pituitary surgery in clinical practice and its relationship with the hydrocortisone replacement doses used.

Methods
Retrospective review of all dynamic testing results post pituitary surgery between 2004 and 2014 in a tertiary centre, and of the medical notes.

Results
101 patients fulfilled the inclusion criteria, out of which 61 (60.4%) were tested with an ITT and 40 (39.6%) with a GST. 27 patients were prescribed glucocorticoids following ITT testing, and 26 following GST. The decision regarding the hydrocortisone dose was made by the trainee or Consultant who had requested the test from clinic. Patients that were prescribed hydrocortisone 20 mg/day had significantly lower peak cortisol levels on dynamic testing compared to patients prescribed 10 mg/day (252 ± 142 nmol/l vs 356 ± 95 nmol/l, P < 0.05) or emergency steroids only (484 ± 45 nmol/l, P < 0.005, no different peak cortisol levels compared to patients prescribed 15 mg/day (313 ± 149 nmol/l). Similarly, patients prescribed 10 mg/day or 15 mg/day had significantly lower dynamic testing peak cortisol compared to patients prescribed emergency hydrocortisone only (P < 0.005 and <0.05 respectively). There was a trend to treat patients who had with radiotherapy with higher doses of hydrocortisone. Most patients continued the steroid dose recommended post dynamic testing and did not require dose changes in stable conditions with a follow-up of 4.4 ± 3 years. On the day of dynamic testing, patients that failed an ITT or a GST had baseline cortisol of 205 ± 112 nmol/l.

Conclusion
Patients diagnosed with hypocortisolism on dynamic testing post-pituitary surgery require variable dose or emergency only glucocorticoid replacement. The peak cortisol level on dynamic testing is useful when deciding the glucocorticoid replacement scheme.

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EP786
Cushing’s Syndrome: An ominous and commonly forgotten cause of hypokalaemia
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Introduction
We report a patient with hypokalaemia secondary to Cushing’s syndrome (CS) to reinforce this commonly forgotten association.

Case report
A 57 years old lady with newly diagnosed hypertension, hyperlipidaemia and diabetes mellitus presented with persistent hypokalaemia for evaluation. She had tense corporis but otherwise did not look Cushingoid. Investigations: K 2.6 (RI: 3.50–5 mmol/l), HCO3 35 (RI: 19–31 mmol/l), Urine K/Cr 8.1. Both renin and aldosterone were suppressed. 24 h urinary free cortisol (UFC) was elevated at 1811 (RI: 59–413 nmol/day); 0800 h cortisol after 1 mg overnight dexamethasone suppression test (DST) was elevated at 1156 nmol/l. The patient denied taking any liquorice or corticosteroids. ACTH dependent CS was made with 1811 (RI: 59–413 nmol/day); 0800 h cortisol after 1 mg overnight dexamethasone suppression test (DST) was elevated at 1156 nmol/l. The patient denied taking any liquorice or corticosteroids. ACTH dependent CS was made with ACTH level of 12.1 pmol/l. Overnight 8 mg DST suppressed the cortisol to more than 171 (RI: 5–121 nmol/l).

Discussion
Activation of MC receptors by cortisol is normally limited due to its conversion to inactive cortisone at the sites of aldosterone action by the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2). In ACTH-dependent CS, cortisol secretion exceeds the metabolic capacity of 11β-HSD2. ACTH inhibits 11β-HSD2 and there may also be hypersecretion of nonaldosterone mineralocorticoids such as deoxycorticosterone (DOC) and corticosterone. Excess MC activity leads to sodium retention, hypertension, hypokalaemia, metabolic alkalosis, low plasma aldosterone and renin activity. Besides CS, other differentials to consider include 11β-HSD2 deficiency, liquorice ingestion, Liddle’s syndrome, DOC-secreting tumour and certain forms of congenital adrenal hyperplasia.
Conclusion
CS presents with hypokalaemia. Earlier diagnosis and management may improve outcome.

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EP787
The effect of pregnancy and lactation on prolactinoma
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Prolactinoma predominantly occurred in young women of reproductive age. But there are limited data about the effect of pregnancy and lactation on prolactinoma progression. We evaluated the safety of dopamine agonists including bromocriptine and cabergoline and pregnancy outcome in prolactinoma patients. Patients diagnosed with prolactinoma who experienced pregnancies were included. Sellar MRI and serum prolactin levels were performed before and after pregnancy and lactation. Total 46 patients with 62 pregnancies were included. Among 62 pregnancies, spontaneous pregnancies analysed 61 (98.3%), while spontaneous abortions occurred in 11 (17.7%). Twenty-one were treated with cabergoline at the time of conception, whereas 28 with bromocriptine. We divided patients into two groups by their changes of adenoma size after delivery; increased (n = 2) or decreased (n = 15). Patients with bigger adenoma size before pregnancy showed significantly increased after childbirth. However, the enlarged adenoma did not cause any clinical problems. Of all, breast-feeding was performed in 38 pregnancies. Mean duration of lactation was 4.9 ± 4.4 months. Among those 38, 16 patients had done MRI follow-up after the lactation. There were decreased adenoma sizes in nine patients, no changes in five patients, while increased only in two patients. In conclusion, breast-feeding is not contraindicated in patients with prolactinoma, especially those who had smaller adenoma.

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EP788
Prevalence of the sleep breathing disorders in untreated and treated patients with acromegaly
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For the purpose to compare sleep breathing disorders (SBD) in untreated and treated patients with acromegaly, we examined 55 patients with acromegaly (18 men and 37 women): 27 patients with newly diagnosed acromegaly, age 56.0 (47.0; 64.0) y.o.; BMI 30.2 (27.8; 34.4) kg/m2, GH levels 12.8 (4.6; 23.0) ng/ml, IGF-1 2.45 (106; 331) % of upper normal limit (UNL), hypertension duration 6.5 (1.0; 14.8) years; 28 patients with treated acromegaly, age 57.0 (47.3; 64.8) y.o.; BMI 30.7 (27.9; 35.0) kg/m2, GH levels 2.1 (1.2; 3.4) ng/ml, IGF-1 14 (7; 21) % UNL, hypertension duration 9.0 (3.0; 10.0) years. Data are expressed in Median (25%; 75%). Respiration monitoring was conducted using device ApneaLink, ResMedInc, Australia. Statistical analysis: SPSv5.2. High index of apnoe-hypopnoe (IAH) was found in 91.9% untreated and in 78.6% treated patients: severe SBD in 51.9% and 46.5% patients (IAH 46.6 (40.8; 57.8) and 47.0 (4.3; 59.0), respectively); moderate SBD – in 25.9% and 21.4% (IAH 21.3 (20.0; 23.0) and 23.2 (18.0; 26.3), mild – in 14.8% and 10.7% (IAH 10.5 (8.3; 12.1) and 5.0 (5.0; 11.0)). The saturation level (normally 94-98%) was decreased in 54.2% untreated and 42.3% treated patients; the average saturation level was 93.0 (90.0; 94.0%) and 94.0 (91.8; 95.3%), correspondingly. Desaturation level (normally 90-98%) was below normal in 91.7% untreated and 83.3% treated patients; the average desaturation was 79.5 (70.3; 86.8) % and 84 (72.3; 88.8) %, respectively. Severity of SBD did not correlated with GH/IGF-1 levels. Moderate correlations were found between IAH and age, IAH and duration of hypertension. Thus, sleep breathing disorders (with high prevalence of severe IAH and significant desaturation) could be found in most of the patients with untreated and treated acromegaly, and regression of SBD after acromegaly treatment is not so significant. Specific methods of apnoe treatment should be considered for patients with acromegaly and SBD.

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EP789
Acrostart: Spanish retrospective study to determine the timeframe to achieve hormonal normalisation with initial Somatuline Autogel10 treatment in acromegaly patients in routine clinical practice
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Introduction
This study aimed to determine the timeframe to achieve hormonal normalisation considering dosing patterns of Somatuline Autogel (SOM, lanreotide) used in clinical practice.

Methods
From March 2013 to October 2013 clinical data from 62 patients with active acromegaly treated with SOM for ≥4 months who achieved hormonal control (GH levels <2.5 ng/ml and/or normalised IGF1 on ≥2 evaluations) at 17 Spanish hospitals were collected into a database. Primary objective was to determine the timeframe from initiating SOM treatment to hormonal normalisation. Secondary objectives included use of health resources, tumour size control, patient satisfaction and adherence.

Results
Non-compliance excluded five patients. Median age of 57 patients was 64 years (23–90), 21 (36.8%) were male, 35 (61.4%) had macroadrenoma, 39 (68.4%) had undergone surgery, 14 (24.6%) had received radiotherapy. Median hormonal values at start of SOM treatment were GH 2.6 ng/ml (95%CI 2.6–7.4), IGF1: 1.6×UNL (95% CI 1.6–2.1). SOM 120 mg was the most frequent initial dose (51% patients), with prolonged interval use (≥6 weeks) in 44% patients. Main starting regimens were 60 mg per 4 weeks (n = 13), 90 mg per 4 weeks (n = 6), 120 mg per 4 weeks (n = 13), 120 mg per 6 weeks (n = 6). 120 mg per 8 weeks (n = 9). Median length of SOM treatment was 68 months (7–205). Hormonal control was achieved in 49 months (95%CI 7.9–20.1). 13 (22.8%) patients managed injections without assistance of health care nurses: 8 (14.0%) were able to self-inject and 5 (8.8%) had injections administered by close relatives. Median number of specialist physician visits until hormonal control was 3 (95%CI 4–10). During SOM treatment tumour shrinkage up to 46.7% was reported in ten patients with available information. 51 (89.5%) patients were ‘satisfied’/‘very satisfied’ with SOM treatment and 49 (86.0%) patients did not miss any doses.

Conclusion
Real-life treatment with SOM led to a fast hormonal control in acromegaly responder patients, with a high treatment adherence and treatment satisfaction, despite disparity of SOM starting doses and interval dosing.

Disclosure
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EP790
Prevalence of the sleep breathing disorders in untreated and treated patients with acromegaly
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There are some data concerning high prevalence of infrasellar extension of somatotropinomas. To reveal any differences expansion of pituitary macroadenomas with various hormonal secretion, we have analyzed MRI data of 175 pituitary macroadenomas: 87 non-functioning adenomas (NFAs), 48 prolactinomas, 43 somatotropinomas. The sizes of pituitary tumour (vertical, sagittal, frontal): NFAs 24 (17.5; 34.5) mm, 23 (17.4; 28) mm, 23 (18; 30) mm; prolactinomas 21 (15; 31) mm, 20 (16; 30) mm, 20 (14; 30) mm; somatotropinomas – 18 (14; 25) mm, 18.2 (14; 24) mm, 17 (14.5; 23) mm. The tumour volume varied: in NFAs from 618 to 68753 mm³ (median 6620 (2636; 14492) mm³), in prolactinomas 565–86871 mm³ (median 5365 (1495; 10316) mm³), in somatotropinomas 352–124501 mm³ (median 3052 (1696; 5727) mm³) (P < 0.001). Prevalence of suprasellar, infrasellar and lateral sellar extensions were: NFAs—94, 62, and 39%; prolactinomas – 75, 64 and 62%; somatotropinomas – 75, 64, and 44%, respectively. Suprasellar tumour growth was predominant in NFAs and prolactinomas but not in somatotropinomas (P < 0.001). Higher frequency of infrasellar growth of somatotropinomas was noted but the difference was not significant in comparison with other tumours (P > 0.05). Obvious prevalent incidence of laterosellar growth of prolactinomas was observed compared with both NFAs (P = 0.002) and somatotropinomas (P < 0.016). Optic chiasm compression according to MRI data was found in 55% of NFAs, 35% of prolactinomas and 19% of somatotropinomas (P < 0.001) and it was correlated with suprasellar growth and vertical size > 18 mm. Thus, in our cohort of patients non-functioning pituitary adenomas have markedly larger volume with predominant suprasellar growth and higher frequency of chiasm compression compared with hormonally active pituitary tumours. Prolactinomas and somatotropinomas did not differ in volume, however, had some differences in growth directions: this is the first data concerning high prevalence of laterosellar extension of prolactinomas, predominant infrasellar growth of somatotropinomas was also observed without significant difference in comparison with other pituitary tumours.
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EP791
Lung function tests in 109 acromegalic patients
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Introduction
Acromegaly is a chronic disease that affects morphology and organ functions. These changes lead to clinically relevant comorbidities. Untreated acromegaly reduces life expectancy by 10 years, mostly due to cardiovascular events, malignancies and respiratory disorders. We present the results of a series of 109 acromegalic patients at a single institution.

Methods
Lung function tests were performed under standardized conditions in patients with acromegaly treated in our outpatient clinic. Normative data was used to compare our patients (measured value) with healthy controls (predicted value); percentage of predicted value was used to perform subgroup analysis. Criteria of cure were IGF1 in the age- and sex-adjusted normal range and random GH < 1.0 µg/dl.

Results
We investigated 109 acromegalic patients without history of pulmonary disease (53 male, 49%) with a mean age of 54.6 (± 13.5) and mean duration of acromegaly of 12.6 years (± 11.6). 20 patients had active, untreated acromegaly at time of assessment. 29 patients were biochemically normalized. Lung function significantly differed from healthy controls in terms of higher volume regarding intrathoracal gas volume, maximal vital capacity, residual volume, total lung capacity, and forced expiratory volume in 1 second. Patients showed signs of obstruction with significantly lower peak expiratory flow and maximum expiratory flow when 75% of the FVC has been exhaled (FEF75/MEF25). 56.5% of patients had a reduced FEF75/MEF25 and 40.4% increased residual volume. There was no significant difference between active and inative acromegaly. Female patients had significantly smaller flow rates of peak expiratory flow, FEF25/MEF75 and FEF50/MEF50.

Conclusions
In our cross-sectional analysis of lung function in 109 patients with acromegaly lung function volumes were increased compared to healthy controls. Patients showed signs of small airway obstruction at time of diagnosis, unchanged in remission. Subclinical airway obstruction was significantly more pronounced in female patients.
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EP792
Thyroid lesions in patients with acromegaly–case-control study
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Introduction
Acromegaly is a disease caused by excessive secretion of growth hormone and subsequently insulin growth factor 1. It is believed that this oversecretion can cause increased prevalence of nodular goiter and thyroid cancer. However, the amount of studies comparing acromegalic patients with control groups is low. The aim of the study was to assess the prevalence of thyroid lesions in patients with acromegaly in comparison with age and sex-matched control group.

Materials and methods
We have searched the medical documentation of patients with acromegaly treated in single endocrine department in the years 2003–2013. The prevalence of thyroid lesions was compared with the group of patients with hormonally inactive adrenal incidentalomas. Thyroid ultrasound is routine procedure performing in every patient hospitalised in our department. Results
patients with acromegaly and 184 patients with incidentalomas were included. mean age was 52.6 and 53.9 years respectively (P = 0.44), percent of women – 60.5 vs 65.2% respectively (P = 0.35). Any thyroid lesions were present in 77.6% of patients with acromegaly and 63.0% with incidentalomas (P = 0.002), multinodular goiter in 66.8% vs 47.8% (P = 0.0002), thyroid cancer in 5.4% vs 2.7% (P = 0.21) respectively. RIs were 1.2 with 95% confidence interval (CI) 1.1–1.4, 1.3 (1.1–1.6) and 2.0 (95% CI 1.7–5.6) respectively. In case of subjects with at least one thyroid lesion, maximal diameter of the biggest thyroid lesion was significantly higher in patients with acromegaly than in control group – median 13.0 vs 9.0 mm (P = 0.0008). Also the mean thyroid volume was significantly higher in acromegalic patients (35.5 vs 17.7 cm³, P < 0.0001).

Conclusions
Structural thyroid abnormalities are significantly more common in patients with acromegaly. Our study, performed on one of the largest described groups of acromegalic patients, confirms that systematic thyroid examination should be important part of follow-up in case of patients with acromegaly.
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EP793
Anterior pituitary hormone deficiencies in primary and surgery related empty sella cases and its effect on quality of life
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Introduction
Primary empty sella (PES) is often found incidentally during neuroradiological studies. Although pituitary function is usually normal in patients with PES, it could be associated with serious clinical conditions including different degrees of hypopituitarism. Post-operative empty sella (POES), the most common group, results from pituitary adenoma and their treatments. Our aim is to compare anterior pituitary functions and quality of life (QoL) with Short Form-36 (SF-36) between patients with PES (total and partial) and POES.
Material and methods
Totally 75 patients (34 partial, 20 total PES and 21 SES) were evaluated. Basal anterior pituitary and its target hormones were measured. When we determined low basal cortisol levels and/ or low insulin like growth factor-1 levels, under insulin tolerance test (ITT) or synacthen test. After the patient gave informed consent to participate in the study, we performed SF-36 to evaluate the QoL.

Results
We classified the patients according to the radiological findings as partial empty sella (group 1), total empty sella (group 2) and POES (group 3). 9 (26.3%) patients in group 1 didn’t have any hormone deficiency however 15 (75%) patients from group 2 and 10 (47.6%) patients from group 3 and 7 (20.6%) patients from group 1 had panhypopituitarism. The ratio of panhypopituitarism was significantly higher in group 2. According to SF-36 scales, Mean score of physical role functioning was significantly higher in group 3. Score of general health perceptions was significantly lower in group 1.

Conclusion
Endocrinological evaluation should be performed during each visit of patients with PES (partial and total) and POES. All hormonal deficiencies should be treated with appropriate medical substitution to maintain the quality of life. QoL in pituitary deficiency were affected in adults, the results showed to physical role functioning and general health perceptions significant difference between groups.

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EP794
Multimodal management of GH-secreting pituitary adenomas – the experience of the endocrinology department Tirgu-Mures, Romania, in the last decade
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Introduction
The diagnostic and therapeutical management of GH-secreting pituitary adenomas has been modified in many aspects in the last decade, and the guidelines also have been considerably changed.

Objective
To evaluate the management of acromegaly applied in an endocrinological clinical unit from Romania, and the efficiency of different therapeutical schemes.

Materials and methods
23 patients with acromegaly, treated and followed-up were included in this study. The positive diagnosis of GH-secreting pituitary adenoma was based on the elevated age-related IGF-1-level, suppressed GH-value >1 ng/ml during oral glucose tolerance test and conclusive hypothalamo-pituitary MRI. The applied different therapeutical schemes (surgery, drugs, radiotherapy and combination), and the efficacy of these – assessed by periodic control of IGF-1-level, suppressed GH-value and MRI – were evaluated.

Results
78.3% of the patients had GH-secreting adenoma, the other 21.7% mixed, GH/PRL-secreting form. At diagnosis the mean suppressed GH-level was 23.2 +/− 6.8 ng/ml, mean IGF-1-value 784.5 +/− 139.4 ng/ml, mean adenoma size 17.7 +/− 2.8 mm. First line therapy was neurosurgery in 14 cases, medical treatment (somatostatine-analogue +/− dopamine-agonist) in six and conventional radiotherapy in three patients, out of which in five cases (21.7%, four after surgery, one after radiotherapy) a good control was achieved. The uncontrolled cases received a second therapeutical procedure, and from them other four cases (17.4%), two reinterventions, one after drug administration and one after radiotherapy) reached a good control. Finally, at eight patients combined multiple therapeutical management (surgery + drug +/− radiotherapy) was applied, and other three cases (13%) been brought under control. During long-term follow-up six patients become non-compliant, and they did not return to reevaluations.

Conclusion
From all the 23 subjects in 52.1% an optimal therapeutic control was achieved with all the applied treatment schemes. Acromegaly could be controlled by monotherapy, mainly neurosurgery in 21.7%, by double treatment scheme in an other 17.4% and by multiple therapeutical combinations in 13% of the cases.

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EP795
Early diagnosis and treatment of pituitary apoplexy in a diabetic pregnant woman
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Introduction
Pituitary apoplexy results from haemorrhagic infarction of a pre-existing pituitary adenoma or within physiologically enlarged gland. Pituitary apoplexy during pregnancy is rare but serious event with significant morbidity and mortality if not recognised in time. Pituitary apoplexy is characterised by sudden onset of headache, nausea, vomiting, visual disturbances, eye movements restricted and varying degrees of pituitary insufficiency and accompanied by change of consciousness may be clinically overt or as subclinical. Our case report describes a woman who presented with pituitary apoplexy in the 27 weeks of pregnancy.

Case report
A 30-year old female patient receiving intensive insulin therapy with diagnosis of gestational Diabetes Mellitus. Patient was presented with severe headache, nausea, and vomiting complaints in the 27 weeks of pregnancy. Patient was hospitalised in with urinary tract infection and hyperglycaemia. Early morning serum cortisol was 3.02 μg/dl (6.2−19.4), FT4: 0.57 (0.93−1.70) ng/dl and TSH: 0.84 μIU/ml (0.34−4.3), other metabolic parameters were within normal limits.

Magnetic resonance imaging (MRI) of the pituitary showed pituitary apoplexy. Patient was started with IV 80 mg twice daily and desmopressin nasal spray twice daily. Patient’s electrolytes was monitored twice daily. The second day was added to patients levotyroxine 50 μg. Surgery was not planned due to risk of loss of baby. Clinical improvement continued in the following days and after supplementation of methylprednisolone, levotyroxine and desmopressin.

Reduction in bleeding site was detected in the control of pituitary MRI. Delivery after 36 weeks of pregnancy was uneventful and a healthy girl was born.

Conclusion
Pituitary apoplexy is a very rare but serious complication that can likely be precipitated by the physiologic changes associated with pregnancy in patients. Because early diagnosis and treatment can and often does result in complete recovery, it is important to recognise and effectively manage this event when it occurs immediately.

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EP796
Changes in mid-regional pro-atrial natriuretic peptide during thirsting separate patients with diabetes insipidus from those with primary polydipsia
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Background
Thirsting is a homeostatic mechanism that is mediated by the renin-angiotensin system and osmoreceptors in the hypothalamus. The water deprivation test as the accepted gold standard in the differential diagnosis of polyuria polydipsia syndrome can be associated with a decrease in extracellular fluid volume in patients with diabetes insipidus (DI). We herein evaluated mid-regional pro-atrial natriuretic peptide (MR-proANP) as marker of extracellular body volume in patients with diabetes insipids compared to primary polydipsia (PP), at baseline and after water deprivation.

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EP797
Cardiovascular risk factors and metabolic parameters in GH deficient patients
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Introduction
GH deficiency in adulthood is associated with increased cardiovascular risk, which is attributed to unfavorable changes in body composition and in metabolic parameters.

Aim
We evaluated haemodynamic, metabolic, inflammatory and coagulation indices that may contribute to the increased cardiovascular risk in GH deficient subjects.

Methods
Twenty-four patients diagnosed with GH deficiency (15 male), with a mean (s.d.) age of 54.3 (2.7), were compared to 15 healthy age, sex and BMI matched, controls. Anthropometric characteristics (BMI and waist-to-hip ratio (WHR)), blood pressure, basal GH, IGF-I, fasting glucose, fasting insulin, Hba1c, lipid levels, ApoA1, ApoB, hs-CRP, fibrinogen, PAI-1, t-PA and circulating thrombomodulin levels were measured in all study participants. Insulin resistance (IR) was calculated by HOMA and, in ten subjects who had undergone an oral glucose tolerance test, insulin sensitivity was also estimated using Matsuda index.

Results
Patients with GH deficiency exhibited a marginally increased WHR and had significantly higher fasting insulin levels, fasting glucose-to-insulin ratio, HbA1c, lipid levels, ApoA1, ApoB, hs-CRP, fibrinogen, PAI-1, t-PA and circulating thrombomodulin levels were measured in all study participants. Insulin resistance (IR) was calculated by HOMA and, in ten subjects who had undergone an oral glucose tolerance test, insulin sensitivity was also estimated using Matsuda index.

Conclusions
A considerable number of risk factors including insulin sensitivity, lipid and lipoprotein levels and pro-thrombotic factors are affected in GH deficient adults. Studies addressing whether GH substitution results in decreased CVD morbidity and mortality are needed so therapy could be more vigorously implemented in such patients.

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EP798
Increased serum levels of the Wnt antagonist Dickkopf-1 (DKK1) and impaired trabecular bone mineral density using QCT scan in acromegalic patients
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Introduction
Acromegaly is associated with increased bone turnover and skeletal fragility. Although the GH/IGF1 system plays an important role in bone homeostasis, effects of GH excess on the Wnt signalling pathway are to be determined. Bone quantitative CT (QCT) provides a volumetric, tridimensional measure of bone mass at the trabecular and cortical level.

Aim
i) To compare volumetric bone density (vBMD) using QCT in patients with acromegaly vs gender-, age-, and BMI-matched controls; ii) to correlate it with the levels of Wnt antagonists, dickkopf factor-1 (DKK1) and sclerostin (SOST), in the same subjects.

Methods
Thirty-one acromegalic patients (17 (55%) men; 18 (58%) with active disease; mean age 48.2±7.5 years (range 28–65 years)) and thirty-two age-, gender- and BMI-matched controls underwent QCT scan using Mindways Software. Serum concentrations of DKK1, SOST, β-crosslaps, procollagen type-1 amino-terminal propeptid (PINP) and osteocalcin were also measured.

Results
vBMD of cortical total hip (CTH vBMD) and trabecular total hip (TTH vBMD) were lower in acromegaly than controls (CTH vBMD, 774±99.4 mg/cm3; P<0.05 and TTH vBMD, 121.4±29.6 vs 142.8±22.8; P<0.01). PINP levels were lower (41.7±20.5 vs 51±21.2 ng/ml; P<0.05), while DKK1 levels were higher (33.7±12.9 vs 26±14.8 pmol/l; P<0.05) in acromegaly patients compared to controls. No intergroup difference in β-crosslaps, osteocalcin and SOST levels was observed. A negative correlation between DKK1 and CTH vBMD (r = -0.382, P<0.01) was observed. A positive correlation between PINP, β-crosslaps, and SOST with CTH vBMD (r = 0.34, r = 0.27, r = 0.26, respectively, P<0.05) was also observed. After multiple regression analysis, DKK1 and disease duration were independent, negative predictors of TTH vBMD (R² = 0.335, P<0.05), whereas female gender was an independent, positive predictor of CTH vBMD (R² = 0.156, P<0.05).

Conclusions
Acromegaly patients exhibit low vBMD on QCT. The Wnt signalling antagonist DKK1 may contribute to the skeletal fragility described in acromegaly. Supported by grants from FIS ISCIII PI 11/00001 and Fundación Merck Serono 2012.

Disclosure
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Metformin-based OAD therapy proved effective in hyperglycaemia associated with pasireotide in patients with acromegaly.

Disclosure

This work was supported by Novartis.

DOI: 10.1530/endoabs.37.EP800

Table 1 Subgroup analysis of the frequencies of hypopituitarism in all patients (n, number of patients; %, frequency).

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pituitary adenomas</td>
<td>62 (41.6%)</td>
</tr>
<tr>
<td>Prolactinomas</td>
<td>13 (8.7%)</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Cushing</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Gonadotrophinomas</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Thyrotropinomas</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Non-secretory adenomas</td>
<td>42 (28.2%)</td>
</tr>
<tr>
<td>Extra-pituitary tumours</td>
<td>13 (8.7%)</td>
</tr>
<tr>
<td>Non-tumoural causes</td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>13 (8.7%)</td>
</tr>
<tr>
<td>Sheehan’s syndrome</td>
<td>59 (39.6%)</td>
</tr>
<tr>
<td>Apoplexia</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Total</td>
<td>n = 149</td>
</tr>
</tbody>
</table>

Note: Frequencies over 10% were represented in bold.

Conclusion

Although non-secretory pituitary adenomas were the most common cause of hypopituitarism in male patients, Sheehan’s syndrome was the leading cause of hypopituitarism in female patients.

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EP800

Metformin-based oral antidiabetic therapy proved effective in hyperglycaemia associated with pasireotide in patients with acromegaly

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Introduction

High affinity binding of pasireotide for both sst5 and sst3 leads to its enhanced efficacy in treatment of acromegaly but results in decreased secretion of insulin, incretins (GLP-1 and GIP) and, to a lesser extent, glucagon. Metformin may be a good option in patients with acromegaly experiencing hyperglycaemia with pasireotide as it improves GLP-1 secretion. We analysed data from a 12-month, Phase III, randomised study in medically naïve patients with acromegaly to better understand the effects of antidiabetic agents used during pasireotide treatment.

Methods

Patients were randomised to pasireotide LAR 40 mg/28 days (n = 176) or octreotide LAR 20 mg/28 days (n = 182) for 12 months. Patients (n = 57) randomised to pasireotide who were not receiving antidiabetic medication at baseline and who initiated such medication during the study were included in this analysis. Three groups were analysed: patients receiving i) metformin alone; ii) metformin + another oral antidiabetic (OAD); and iii) insulin + OAD.

Results

Metformin was the most commonly initiated antidiabetic; metformin alone (n = 24), metformin + another oral antidiabetic (OAD; n = 19) and insulin + OAD (n = 10). Mean (s.d.) fasting plasma glucose (FPG) and HbA1c at baseline were 9.4 (1.7) (mg/dl and 5.8% (0.4%) for metformin alone, 9.9 (2.1) (mg/dl and 5.8% (0.4%) for metformin + another OAD, and 10.6 (1.9) (mg/dl and 6.1% (0.5%) for insulin + OAD. Mean (s.d.) FPG values at month 3 were 131.0 (37.2), 153.2 (41.6) and 170.0 (88.6) mg/dl, and at month 12 were 126.7 (17.4), 132.6 (25.0) and 137.1 (31.7) mg/dl in the three groups. HbA1c values were 6.6% (0.5%), 7.0% (1.0%) and 8.7% (1.9%) at month 3, and 6.6% (0.7%), 6.7% (0.6%) and 7.2% (1.2%) at month 12.

Conclusions

At month 12, patients treated with metformin monotherapy or in combination with OAD agents had a mean HbA1c that met the ADA/EASD goal of <7%.
EP802
A case of idiopathic granulomatous hypophysitis that was initially treated as a prolactinoma
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Idiopathic granulomatous hypophysitis is a very rare inflammatory disease of the pituitary gland. Primary hypophysitis represents a difficult diagnostic challenge because it can imitate pituitary adenomas clinically and radiologically. The diagnosis is usually made histologically by hypophysectomy. We herein present a rare case of idiopathic granulomatous hypophysitis diagnosed primarily by pituitary biopsy.

Case
A 50-year-old female patient presented with headache, visual loss and menstrual irregularities over the preceding year. At her first visit at another hospital, TSH level was normal but prolactin level was high (PRL: 115 ng/ml). In her visual field examination, a near total defect on right eye and a peripheral visual field defect on left eye were detected. Pituitary MRI revealed a 17 × 9 × 12 mm macroadenoma extending to optic chiasm. Cabergoline therapy was started. When she applied to our clinic 3 months later, pituitary MRI demonstrated a 6 mm microadenoma and her vision complaints were disappeared; but hypothyroisim and secondary hypothyroidism were detected. Replacement therapies were started and cabergoline was stopped. This unexpected development of pituitary insufficiency necessitated a re-evaluation of MRI screenings. Because our decision was in favor of a possible hypophysitis, trans-sphenoidal pituitary biopsy was performed. Pituitary biopsy demonstrated non-necroting granulomatous hypophysitis. Possible secondary causes were investigated and no evidence was found. The final diagnosis was idiopathic granulomatous hypophysitis. We decided to follow-up the patient and replacement therapies were continued. The patient had no further complaints.

Conclusion
Idiopathic granulomatous hypophysitis, which is a very rare disease, diagnosed by pituitary biopsy is the main characteristic of our remarkable case. In patients with pituitary insufficiency, considering hypophysitis is a crucial clinical decision especially if they have specific radiological findings because it is highly possible to treat these patients medically and avoid hypophysectomy.

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EP803
Transsphenoidal surgery of pituitary adenomas in 491 clinical cases: the retrospective single-centre study
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Introduction
The number of studies on the incidence and outcomes of surgical treatment for pituitary adenomas is still limited, despite that pituitary tumours are one of the most frequent intracranial tumours.

The aim of this study
To evaluate clinical features of transsphenoidally operated pituitary adenomas (PA) and perioperative results of the treatment.

Materials and methods
This is a retrospective single institution study of 491 patients. Data were collected from medical records of patients operated during the period 1995–2014 at the Hospital of Lithuanian University of Health Sciences due to functioning and non-functioning micro or macroadenomas. The series consisted of 357 (64, 91%) female and 193 (35, 09%) male patients, with a mean age of 49.95 ± 16.4 year (range 18–85 year).

Results
The study included 227 non-functioning and 264 functioning adenomas: 103 were GH, 122 prolactin (PRL), 32 ACTH and severe TSH secreting adenomas. Female patients were significantly younger than male patients (P < 0.02). Gross total resection as ascertained by surgeon just after the operation was achieved in 92 (40.71%) cases of non-functioning adenomas, 62 (64.58%) cases of GH, 64 (55.17%) cases of PRL, 24 (85.71%) cases of ACTH, and 3 (42.86%) cases of TSH secreting adenomas. According to the size the non-functioning tumours were significantly large than functioning adenomas. Tumour type and size directly influenced surgical outcome. The highest possibility for total tumour removal was detected in the case of ACTH secreting adenomas (P < 0.001) and lowest in non-functioning adenomas (P < 0.001). Surgical intraoperative rupture of membrane selle turcique and liquorhea occurred in 16.51% and no major intraoperative complications were observed.

Conclusion
Our centre data confirm effectiveness and safety of transsphenoidal surgery for PA and the best prognosis for ACTH secreting PA.

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EP804
Pharmacokinetic and pharmacodynamic analyses of pasireotide LAR from a randomised, phase III study in patients with inadequately controlled acromegaly
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Introduction
A 24-week, PhIII, randomised study (PAOLA) demonstrated superior efficacy of pasireotide long-acting release (PAS-LAR; 40 and 60 mg) vs continued treatment with octreotide LAR 30 mg or lanreotide Autogel 120 mg (15.4%, 20.0% vs 0% ) at providing biochemical control (GH <2.5 µg/l and normalized IGF-1) in patients with acromegaly inadequately controlled on first-generation somatostatin analogues. Results from PK/PD analyses of PAS-LAR are reported here.

Methods
Relationship between PAS plasma concentration/efficacy endpoints (GH and IGF-1) and PAS exposure/safety (FPG, ECG, and liver function tests) were analysed. Dose-proportionality was explored and possible covariate effects were determined using linear mixed-effects models.

Results
A steady-state PAS concentration was achieved following three consecutive monthly injections. PAS exposures were approximately dose proportional for the tested dose range (40–60 mg). Gender, age, and baseline total bilirubin levels were statistically significant PK covariates for PAS concentration but without clinically significant impact. A clear exposure-response relationship was observed between PAS concentration and efficacy endpoints. Estimated maximum GH and IGF-1 suppression (mean ± 6.5%) was 83.0 ± 6.5% and 67.1 ± 5.8%, respectively. Estimated effective concentration of PAS to suppress GH to 2.5 µg/l was 12.3 ± 3.3 nm/l; to suppress IGF-1 to 1 x ULN required higher PAS concentration (42.3 ± 16.6 nm/l). These results were aligned with clinical finding of higher response rate for GH vs. IGF-1 with 40 and 60 mg (40 mg: 35.4% vs 24.6%; 60 mg: 43.1% vs 26.2%). A 1.5-fold increase in PAS trough concentration (40–60 mg dose) was associated with a 54, 44, and 51% increase in the odds of GH+IGF-1, GH and IGF-1 responses, respectively; corresponding increase in the odds of having hyperglycaemia was only 36%.

Conclusions
A positive relationship between PAS exposure and efficacy supported the clinical observations of higher GH and IGF-1 response rates with higher dose (60 mg vs 40 mg). These results are aligned with the clinical findings of a positive benefit/risk profile for PAS-LAR treatment in this patient population.

Disclosure
This work was supported by Novartis.

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**EP805**

**Pituitary apoplexy in GH-deficient adults treated with GH – a KIMS database retrospective study**

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**Background**

Pituitary apoplexy (PitApo) has significant associated-morbidity and its management is not yet standardised.

**Aim**

To describe prevalence and characteristics of PitApo patients in GH deficient (GHD) patients compared with two control populations.

**Patients and methods**

Patients with ‘infarction-apoplexy’ GH aetiology code were identified from Pfizer International Metabolic Database (KIMS). Baseline characteristics, GH dosage and 1-year response to GH replacement of PitApo patients were compared with non-functioning pituitary adenoma (NFPA, n=3828) and Sheehan’s syndrome (n=495) control groups.

**Results**

We identified 151 PitApo patients (0.96% of 15,809 GHD patients), including eight PitApo reported as adverse events during KIMS. Median age at GHD diagnosis was lower in PitApo than NFPA (47.8 vs 51.8 years, P<0.01) and higher than Sheehan’s patients (42.5 years, P<0.001). Gender distribution was similar in PitApo and NFPA groups (68.2% vs 60.8% males). There were no differences in dose between groups regardless of oestrogen use. The proportion of GH-naïve/semi-naïve patients with normal IGF-I after 1 year of GH replacement was similar between PitApo and NFPA (80.4% vs 82.5%) and lower in Sheehan’s (57.8%, P<0.0001 vs PitApo). Median IGF-I SDS 1-year increase was similar in PitApo and NFPA (1.61 vs 1.92) and higher in Sheehan’s (2.39, P=0.05 vs PitApo). Mean age/gender-adjusted serum total cholesterol decreased from baseline in PitApo (~0.76 mmol/L) vs NFPA (~0.32 mmol/L, P<0.05) and Sheehan’s patients (~0.19 mmol/L, P<0.05), while LDL- and HDL-cholesterol changes did not differ. AGHDA-QoL score reduction (indicating improved QoL) was similar in PitApo and NFPA (~4.33 vs ~3.76 points) and higher than Sheehan’s patients (~1.58 points, P<0.01 vs PitApo).

**Conclusions**

In this large cohort of patients with pituitary apoplexy, representing <1% of GHD patients overall, GH dose and treatment effects were comparable to NFPA controls, except for greater reductions in serum lipids, while Sheehan’s controls attained normal IGF-I less frequently and their QoL improved less.

**Disclosure**

KIMS is sponsored by Pfizer, Inc. SR is a Marie Curie IEF postdoctoral fellowship recipient (grant no. 303006/2011).

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**EP807**

**Macroprolactinomas invasive and its response to treatment in women. Cali - Colombia cohort study**

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**Background**

Orolactin-producing tumours are the most frequent pituitary tumours, representing 40% of these tumours, with an annual incidence of 6–10 cases/million. <10% are macroprolactinomas, which vary by age and gender, with female to male ratio of 10:1, however, less diagnosed in this population group.

**Objective**

To describe clinical features and therapeutic response of 30 women with invasive macroprolactinoma.

**Methods**

Follow a cohort of 30 patients was performed, aged 18–47 years, in Imbanaco Endocrine Clinic Medical Center in Cali, Colombia, between 2002 and 2012. Demographic and clinical characteristics were analysed; signs, symptoms, hormone levels, surgery and complications. Univariate analysis to estimate proportions and measures of central tendency was performed according to the nature of the variable. Treatment success was defined as a decrease in time macroprolactinoma size, measured by NMR and decrease in serum prolactin. Parametric tests were used to compare serum prolactin and tumor size Fisher Snedecor’s F was applied.

**Results**

The mean age was 35 years, and BMI 28. The symptoms were; 96.7% headache, menstrual disorders, 90, 80% hypopituitarism, visual disorder 76.7% decreased libido 73.3% Galactostomas/asthenia 70%, infertility 60, 30% unilateral amaurisus. Trans-cranial 16.7, 43.5% trans-sphenoidal surgery, 23% of patients started with bromocriptine, of these 10% used it as monotherapy, 13% remaining, cabergoline should start. 86% received only cabergoline. Regarding complications presented 20% empty sella, 3.3% rinoliquia. With statistically significant differences (P<0.0001) measurements at 6 and 12 months in the three diameters relative to the benchmark, like serum prolactin.

**Conclusion**

Interventions Patients were successful in 100% of cases.

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EP808
Trial design of phase IIIb, open-label, single arm study to evaluate efficacy and safety of pasireotide LAR in patients with inadequately-controlled acromegaly despite treatment with first-generation somatostatin analogues
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Introduction
The present study is designed to evaluate the efficacy and safety of pasireotide-long-acting release (LAR) in patients with acromegaly inadequately controlled after ≥3 mo treatment with the maximal approved doses of first-generation SSAs.

Methods
Phase IIIb, multicentre, single-arm, open-label study.

Patients
Adults (N=112) with inadequately controlled acromegaly (mean GH>1 µg/l and IGF-1>1.3xULN) despite receiving octreotide-LAR (30 mg/40 mg depend- ing on the country) or lanreotide-ATG (120 mg) for ≥3 mo.

Design
Run-in phase (≥3 mos): patients on octreotide-LAR 30 mg despite the availability of the 40 mg dose at the time of screening will enter a run-in receiving three injections of octreotide-LAR 40 mg/28 day. Core phase (wk36-36): starting dose of pasireotide-LAR: 40 mg/28 day. GH and IGF-1 evaluated every 12 week and dose increased to 60 mg/28 day in uncontrolled patients (mean GH>1.0 µg/l and/or IGF-1>ULN) if no tolerability issues. Dose will remain unchanged in biochemically controlled patients. Dose decrease is permitted for safety reasons. During the extension phase (wk36-72), concomitant medications used to treat acromegaly are allowed if patients are uncontrollable on pasireotide 60 mg/28 day. Safety and tolerability will be assessed throughout the study.

Endpoints
Primary: proportion of patients with GH<1 µg/l and IGF-1<ULN at wk36; supporting analyses for primary endpoint will be performed in two patient sub-groups by mean GH level at screening (GH: 1–2.5 µg/l, GH>2.5 µg/l).

Secondary: change in mean GH (five-point profile over a 2 h period), IGF-1, GH level at screening with GH 1–2.5 µg/l or normal IGF-1 alone.

Conclusions
This study will evaluate efficacy and safety of pasireotide-LAR in patients with inadequately controlled acromegaly after ≥3 mo treatment with maximal approved doses of first-generation SSAs. In particular, a new patient population with GH 1–2.5 µg/l not studied in the PAOLA study will be evaluated.

Disclosure
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EP809
Thyrotropinaemia – not just hyperthyroidism
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Thyrotropinaemia is a very rare cause of hyperthyroidism. In October 2014 a 41-year-old male patient was examined for anaemia and diarrhoea. Abdomen CT scan, gastroscopy, colonoscopy and parasite tests did not reveal any abnormalities. The patient had lost 18 kg 7 years ago and his weight had been stable since then (BMI 21.3 kg/m²). The laboratory tests revealed high TSH, normal T4 and low cortisol level. The patient referred to our department presented with diarrhoea, velvet skin, loss of facial, chest, axillary and pubic hair; he admitted occasional heart palpitations. The results of insulin tolerance test showed secondary adrenal insufficiency. Other laboratory results were: TSH 13.56 µU/ml (no increase in TRH stimulation test), T3 12.57 pmol/l, T4 55.55 pmol/l, low FSH, LH, DHEA-S, testosterone, GH and IGF-1 levels. Pituitary MRI demonstrated a solid intra- and suprasellar pituitary macroadenoma (25 mm) with sphenoïd and cavernous sinus invasion and optic chiasma dislocation. Thyroid ultrasound showed low echogenicity of thyroid gland. Densitometry revealed osteoporosis. Diarrhoea resolved on gluten-free diet (suspected coeliac disease). ASCA antibodies were positive (suspected Crohn disease). The gastroenterological diagnosis has not been clearly stated. We introduced octreotide injections every 4 weeks, hormonal replacement and otophosis therapy. TSH, T4 and T3 still remain above upper limit of normal. Control pituitary MRI will be performed in February 2015 and the patient will be qualified for neurosurgical treatment. We conclude that clinical image of thyrotropinaemia may be confusing due to coincident symptoms of pituitary deficiency and potential concomitant diseases. Optimal diagnosis and treatment require a multidisciplinary approach.

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EP810
Pasireotide long-acting release maintains biochemical control in patients with acromegaly: results from the extension of randomised, Phase III, PAOLA study
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Introduction
This study will evaluate efficacy and safety of pasireotide-LAR in patients with inadequately controlled acromegaly (n=198) demonstrated superior efficacy of pasireotide-long-acting release (LAR; 40 mg/28 day) in biochemical control (GH<2.5 µg/l and normalized IGF-I) vs continued treatment with octreotide LAR 30 mg/lanreotide Autogel 120 mg (15.4% and 20.0% vs 0%). Here we report preliminary data from the extension phase of PAOLA at wk28.

Methods
Pasireotide-LAR (40 mg/60 mg) patients who were biochemically controlled at wk24 (core phase) continued with the same double-blind pasireotide LAR dose whereas uncontrolled patients started open-label pasireotide LAR 60 mg. Uncontrolled patients in the active-control group (octreotide LAR/lanreotide Autogel) patients crossed over to open-label pasireotide LAR 40 mg. Key efficacy endpoints at extension wk28 were i) proportion of patients with biochemical control ii) proportion of patients with GH<2.5 µg/l or normal IGF-I alone. Safety and tolerability were evaluated.

Results
A total of 173 patients entered the extension (pasireotide LAR 40 mg, n=57; pasireotide LAR 60 mg, n=54 by randomised dose; crossover, n=62). The preliminary analysis at wk28 in all patients achieving that time point, including early discontinuation showed that the proportion of patients with i) biochemical control was 18.4% (9/49), 33.3% (15/45), and 20.0% (10/50) ii) GH<2.5 µg/l was 38.8% (19/49), 46.7% (21/45), and 42.0% (21/50); normal IGF-I was 32.7% (16/49), 37.8% (17/45), and 24.0% (12/50), in the pasireotide LAR 40 mg-, pasireotide LAR 60 mg-, and crossover arm, respectively. Safety findings were consistent with the ones in the core phase; most common adverse events were hyperglycaemia, diabetes mellitus, cholelithiasis, and diarrhoea.

Conclusions
The preliminary data in patients achieving wk28 indicate that pasireotide LAR maintained biochemical control during the extension in patients with inadequately-controlled acromegaly: ~20% of the active-control patients achieved biochemical control after crossing over to pasireotide in the extension.
No new safety signals were identified during the extension. These findings suggest that pasireotide LAR is a viable, long-term treatment option for patients with acromegaly.

Disclosure
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EP811
Ongoing, open-label, multicenter, expanded-access study demonstrating the safety and efficacy of pasireotide se in patients with Cushing’s disease
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Background
Pasireotide (Signifor®), a multireceptor-targeted somatostatin analogue, was initially approved in Europe and the USA in 2012 for treating adult patients with Cushing’s disease for whom surgery is not an option(has failed. This ‘expanded-access’ study allowed patients to receive pasireotide until regulatory approval was obtained in their country, and collected further safety/efficacy data. Here we report an interim analysis of this ongoing study.

Methods
Adult patients with confirmed Cushing’s disease were enrolled; all had mean 24-h UFC obtained in their country, and collected further safety/efficacy data. Here we report an interim analysis of this ongoing study.

Results
As of 31/7/14, 97 patients enrolled (mean age 42.2 ± 12.8 years). Median exposure to pasireotide was 23.6 weeks (range 1–131). 22 patients (22.2%) are still on study and 29 (29.9%) have completed; 46 (47.4%) discontinued: primary reasons were AEs (n=16), unsatisfactory therapeutic effect (n=13), consent withdrawal (n=13) and other (n=4). Most AEs were mild/moderate; most common: nausea (n=48; 49.5%), diarrhoea (n=46; 47.4%), hyperglycaemia (n=38; 39.2%). At weeks 12, 24 and 48: 35/71 (49.3%; 95% CI 37.2–61.4), 26/49 (53.1%; 38.3–67.5) and 11/27 (40.7%; 22.4–61.2) patients had UFC decrease ≥50% from baseline.

Conclusions
This study provides further evidence that pasireotide effectively decreases UFC levels and improves clinical signs/symptoms, with a generally favourable safety profile, in patients with Cushing’s disease.

Disclosure
This work was supported by Novartis.

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EP813
Cone beam computed tomography reveals altered trabecular bone structure in acromegaly
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Over the last years, there has been evidence that acromegaly may cause skeletal fragility with high risk of vertebral fractures. The diagnostic approach to this complication is still a matter of uncertainty, since DXA measurement of bone mineral density (BMD) does not provide reliable information on fracture risk in acromegaly. The cone beam computed tomography (CBCT) technique offers three-dimensional images for the radiographed area with the advantage to use non-dedicated equipments as compared to the peripheral Quantitative Computed Tomography. The aim of this study was to investigate whether a non-dedicated CBCT system may provide information on the skeletal abnormalities caused by acromegaly. Twenty-two patients with acromegaly (12 females, ten males; mean age 62 years, range 25–72) and 16 healthy control subjects (six females and ten males; mean age 59 years, range 25–68) were studied using high resolution CBCT system (Newtom 5G; QR, Verona, Italy) at the distal radius. All acromegaly patients were also evaluated for DXA BMD at lumbar spine, total hip, femoral neck and distal radius. Patients with acromegaly showed lower trabecular bone volume fraction (BV/TV) (P=0.001) and mean trabecular thickness (Th.mean) (P=0.001) and greater mean trabecular separation (Sp.mean) (P=0.01), without significant difference in cortical thickness (P=0.47) as compared to the control subjects. In acromegaly patients, the duration of active disease significantly correlated with BV/TV (r: −0.69; P=0.001), Th.mean (r: −0.46; P=0.05) and Sp.mean (r: 0.47; P=0.04). In acromegaly patients, the BMD at distal radius significantly correlated with cortical thickness (r=0.56; P=0.007), whereas the BMD at either skeletal site was not significantly correlated with the trabecular parameters. In acromegaly patients, the distal radius CBCT reveals significant alterations of physiological trabecular bone structure which may be responsible for their high risk of fragility fractures even in the presence of normal BMD.

Disclosure
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EP814
Cabergoline test as a predictor for long term therapy management of hyperprolactinaemia
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Objective
To determine if the response to one single dose of 0.5 mg cabergoline (CAB) can be used as predictor for choosing personalized therapy of hyperprolactinaemia. Although CAB is a selective, long half-life D2-receptor agonist against some patients proved to be resistant with minimum to no response in serum prolactin and tumour shrinkage, even after a few months of treatment.

Patients and methods
A dose of 0.5 mg CAB was administered orally to a number of 53 naive patients, in a prospective interventional study. Based on hyperprolactinaemia two groups were selected: the first group of 38 patients with prolactinoma and a second group of 15 patients with other causes of hyperprolactinaemia, who served as control. In the prolactinoma group all cases were prospectively evaluated, starting a maintenance phase with 2–3 mg cabergoline twice a week for at least 6 months. This second phase allowed us to divide the prolactinoma group into sensitive and resistant cases: 31 proved to be sensitive and seven resistant to CAB, when comparing the results of serum prolactin dosage and tumour shrinkage on CT/MRI scan. The main test consists of a first phase when a single dose of CAB is administered and the serum prolactin is measured at basal, 12 and 48 h comparing these results. For a more complete understanding and analysis of linkage mechanism the plasma CAB levels were also measured using a mass-spectrometry based method. The instrumental analysis was performed on a HPLC tandem mass-spectrometer in the multiple-reaction monitoring method (MRM).

Results
CAB determined prolactin decrease in both sensitive and resistant cases but with a significant difference. In sensitive prolactinoma the decrease showed to be from 2781 to 1099 ng/ml at 12 h (which means almost with 60%, P<0.001), 1977.1 ng/ml at 24 h and 843.63 at 48 h. The highest decrease was registered at 12 h after CAB administration. In resistant prolactinomas, the decrease went from 3675.7 ng/ml basal value to 2043 ng/ml at 12 h, 1679.71 at 24 h and 1586.6 ng/ml at 48 h (which means lower than 45% in the first 12 h). In the control group the decrease was also much smaller. In the follow up time: one patient with small response at CAB test proved to be long-time therapy responsive and another one with prolactin decrease on CAB test, proved to develop partial response in long time treatment. Meanwhile, CAB pharmacokinetics showed the highest value at 12 h, which was 9.50 pg/ml with 6.44 pg/ml at 24 h and 4.73 pg/ml at 48 h.

Conclusions
CAB test can provide information about the sensitivity to treatment for a better future management and good results, which is allowing patients to receive personalized therapy in adapted method and time duration. Anyway, further studies with larger study population should be done in order to completely understand all possible determinants of a better or a more accurate therapy response.

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EP815
Renal function in acromegaly
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Introduction
Acromegaly is a rare disease resulting from GH excess mostly due to pituitary adenomas. It is associated with changes of most organ systems and multiple comorbidities. The impact of GH and IGF-I excess on renal function in acromegaly is unclear.

Methods
We investigated 66 acromegalic patients from our outpatient clinic (32 female, 34 male, mean age 61.5±12.9 years, women 10 years older than men). The renal function was assessed by blood and urine tests, ultrasound and blood-gas analysis.

Results
38 patients were considered biochemically controlled according to latest recommendations on criteria for cure of acromegaly (IGF-I in age- and gender-specific reference range, random basal GH <1 ng/ml). 12 patients were partially controlled (IGF-I up to 1.3 times elevated), 16 biochemically active. 61% of the patients have hypertension (68% of the controlled, 75% of the partially and 31% of the uncontrolled patients), 21% of the patients presented with diabetes mellitus, 11% have both. The distribution between the sexes was balanced. According to the Cystatin C formula (GFR(CysC)=77.24×Cystatin C−1.263) 39 patients (59%) presented with reduced glomerular filtration rate (GFR < 90 ml/min), 50% of the patients have a chronic kidney disease stage 2 (GFR 60–89 ml/min), 9% stage 3 (GFR 30–59 ml/min). Despite their higher age the median GFR of the female patients is 4 ml/min higher (82.4 vs 86.4 ml/min). The median GFR of hypertensive patients is 21.6 ml/min lower than in patients without hypertension (80.8 vs 102.4 ml/min). There is no significant difference between the GFR of controlled, partially and not controlled patients in our patients (81.9 vs 89.5 vs 84.1 ml/min).

Conclusion
We found a reduced renal function (GFR <90 ml/min) in 59% of acromegalic patients. The disease activity has no effect on GFR as determined by Cystatin C formula.

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EP816
Successful treatment of huge pituitary macroadenoma secreting TSH and GH
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Introduction
The mixed tumor which secretes an excess of both GH and TSH causing acromegaly and hyperthyroidism is rare. The main problem is the late diagnosis, especially in men, even 10 years after the occurrence of the first symptoms.

Case report
A 53-year-old men, was admitted to the our department, with complaints of excessive sweating and enlargement of the hands. His medical history included arterial hypertension. Past medical history revealed thyroidectomy 20 years ago. Physical examination showed typical signs of acromegaly and nodules in both lobes of the thyroid gland. Performed laboratory test revealed elevated plasma concentrations of the PRL levels: 79.52 (0–29 ng/ml), IGF-I: 593 (87–267 ng/ml) and lack of the suppression of GH after 75 g glucose (6.67 ng/ml). Additionally, we observed central hyperthyroidism: fT 4: 3.09 (0.7–1.48 ng/ml), fT 3: 17.49 (1.45–3.48 pg/ml) and TSH level: 6.095 (0.35–4.94 mU/ml) with normal anti-TPO: 0.4 (0–4.1 ng/dl). Diagnosis was confirmed by dynamic testing with TRH. An ultrasound scan of the thyroid showed a multinodular goitre. MRI revealed a large pituitary macroadenoma measuring 5×6×6 cm with left cavernous and sphenoid sinus invasion, with compression of the optic chiasm, the third ventricle as well as the brainstem. Firstly, patient was treated with thiamazol, octreotide LAR and bromocriptine during 6 months. Then, he proceeded twice to the transphenoidal resection of the pituitary macroadenoma with consecutive partial reduction of the tumor mass. After neurosurgery laboratory signs of hyperthyroidism resolved but serum GH was still elevated. Currently, the patient is under octreotide LAR therapy.

Conclusions
We presented an unusual case with a huge pituitary macroadenoma secreting TSH and GH who was successfully treated with transphenoidal adenomectomy. This case showed that despite of symptoms and size of mixed tumour, diagnosis could be missed for the long time. On the other hand, the proper preparation for surgery, lets avoid the complications during the perioperative period.

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EP817
Management of Cushing’s disease: single centre experience
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Introduction
Cushing’s disease (CD) is an uncommon condition of excess endogenous glucocorticoids caused by ACTH secreting pituitary corticotroph adenoma.
The purpose of this study is to review therapeutic outcomes and comorbidity of patients with CD in a single centre.

Methods
We conducted a retrospective study of 33 patients with CD undergoing transsphenoidal surgery from January 2007 to February 2014. (27 female and six male, median age 38 years, range 18–71 years). The diagnosis of Cushing’s syndrome was established on the basis of the patient’s history, characteristic clinical features and laboratory data, including elevated 24-h urinary free cortisol (UFC) level, lack of serum cortisol suppression after suppression tests (1-mg overnight dexamethasone suppression test and/or 2 mg–2 days dexamethasone suppression test) and elevated midnight cortisol level. In 28/33 patients tumor was visualised on MR of sellar region, while in five it was diagnosed using an inferior petrosal sinus sampling.

Results
Ten patients had macroadenoma, the remaining 23 had microadenoma. Twenty-one patients (63.6%) had hypercortisolism, 17 (51.5%) dyslipidemia, while 7 (21.2%) had type 2 diabetes or Impaired Glucose Tolerance. Median follow-up period was 58.3 months. Remission after transsphenoidal surgery was achieved in 78.8% of patients, while seven patients failed to achieve disease remission. They were treated with second-line treatment modalities (second operation, radiotherapy, bilateral adrenal enucleation and/or ketocamazole). One patient rejected all treatment modalities after surgery.

Conclusion
Cumulative remission after all treatment modalities was achieved in 93.9% patients. Two female patients had recurrence of hypercortisolism. The results of our Centre are comparable to leading centers in the world.

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EP818
Post-operative serum cortisol levels as predictors of recurrence in Cushing’s disease
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Introduction
Cushing’s disease (CD) is characterized by increased secretion of ACTH often as a result of a pituitary adenoma. The surgical success rates after transsphenoidal pituitary surgery (TSS) range from 53 to 96% in different centres. Postoperative cortisol levels have been proposed as the standard criteria for prediction of surgical remission however, this variable is subject of a variety of interferences.

Objectives
Evaluate the potential of post-transsphenoidal pituitary surgery cortisol levels to predict surgical remission and recurrence of CD.

Methods
Retrospective cohort study of patients with clinical and biochemical diagnosis of CD, submitted to TSS and followed in our centre between 1977 and 2013 (n=34).

Results
Patients who lost follow-up or with insufficient data on their personal records were excluded (n=51). Statistical analysis: SPSS (21).

Thirty three patients, 29 (87.9%) women, with a median age of 33 years were included. All patients underwent TSS as first treatment option and were followed postoperatively during a median period of 8 (1–28) years. Eighteen (57.8%) patients achieved disease remission after the first treatment, 11 (33.3%) presented postoperatively during a median period of 8 (1–28) years. Eighteen (57.8%) included. All patients underwent TSS as first treatment option and were followed

Conclusion
Ten patients had macroadenoma, the remaining 22 had microadenoma. Two female patients had recurrence of hypercortisolism. The results of our centre are comparable to leading centers in the world.

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EP819
Endocrine manifestations of Langerhans cell histiocytosis
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Introduction
Langerhans cell histiocytosis (LCH) is a rare disorder characterized by proliferation/accumulation of cells phenotypically similar to skin Langerhans cells. Clinical presentation and aggressiveness are very heterogeneous, from benign to disseminated forms that cause significant morbi-mortality, particularly endocrine failures.

Case 1: A 15-year-old Caucasian woman presented with a 14-month history of headaches, secondary amenorrhea. She reported polyuria and polydipsia in the last 2 years. Secondary evaluation revealed hypogonadism and central obesity and a 1 cm suprasellar lesion. Surgical excision of the lesion was performed, though histologic examination was inconclusive, and panhypopituitarism developed after surgery. Radiotherapy was prescribed due to persistent disease. Two years later, biopsy of recurrent vulvar ulcers revealed HCL. Subsequent studies showed active disease in the vulvar region, thyroid and hypothalamic–pituitary axis, which remitted after several cycles of vulvar radiotherapy, and systemic chemotherapy with prednisolone, metothrexate, and vinblastine (PDN/MTX/VBA).

Case 2: A 37-year-old Caucasian man presented with a 6-month history of otalgia, otorrhea, weight loss, and skin brown maculo-papular rash. He reported polyuria and polydipsia in the previous 5 years. Secondary evaluation revealed panhypopituitarism and a suprasellar mass of 2 cm. Temporal bone biopsy revealed HCL. Patient was treated.

Case 3: A 60-year-old Caucasian woman presented with 6-month history of jaw pain and weight loss. Secondary evaluation revealed polyostotic HCL and the patient was treated with zoledronic acid. Three years later the patient complained of headaches, polyuria, and polydipsia. Complimentary evaluation revealed diabetes insipidus, hypogonadism hypogonadotropic, central hypothryosidism, and pituitary stalk enlargement. All patients required permanent hormonal substitution for the failed HPA sectors.

Conclusion
All cases described had hypothalamo-pituitary axis involvement with pituitary failure. The dominant manifestation was diabetes insipidus. If not treated promptly LCH may have a considerable morbidity with permanent endocrine failures, that require proper hormonal substitution. Relapses may occur and appropriate follow-up is recommended.

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EP820
High BMI in female patients with prolactinomas
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We analysed BMI of 270 female patients: 148 with hyperprolactinaemia (non-tumoural hyperprolactinaemia, n = 46; microadenomas, n = 56; and macroadenomas, n = 46), 55 with isolated central hypogonadism, 67 with hypopituitarism. Additionally, 53 healthy women of reproductive age and 51 postmenopausal women were examined. In patients with hyperprolactinaemia median prolactin levels were 5147 (1124; 2185), 1490 (1050; 2280), and 3100 (1790; 18840) mE/l, respectively. The highest BMI was noted in patients with macroprolactinomas and 32 (26; 46; microadenomas, 23 (22; 34.5) kg/m² – in microprolactinomas and 32 (26; 35) kg/m² – in macroprolactinomas was 22.5 (20; 23) kg/m² in non-tumoural hyperprolactinaemia, 23 (22; 34.5) kg/m² in microprolactinomas and 32 (26; 35) kg/m² – in macroprolactinomas was 22.5 (20; 23) kg/m² in non-tumoural hyperprolactinaemia, 23 (22; 34.5) kg/m² in microprolactinomas and 32 (26; 35) kg/m² – in macroprolactinomas was 22.5 (20; 23) kg/m² in n...
it was significantly greater than BMI in other hyperprolactinaemic and non-hyperprolactinaemic subgroups (P<0.001 for all). Thus, we conclude that hyperprolactinaemia per se is not a risk factor for obesity in women. Prolactin-secreting pituitary lesions lead to the higher rate of increased BMI, and macroprolactinomas are more powerful risk factor for obesity than physiological menopause or hypopituitarism.

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**EP821**

Study of the prevalence and related factors in the withdrawal of medical treatment macroprolactinomas

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Introduction

The prolactinoma is the most common functioning pituitary tumour. There are few long-term studies on the optimal duration of treatment with dopamine agonists prolactinoma to ensure healing without recurrence after stopping the medication and do not provide a consensus on it or on withdrawal criteria treatment.

Objectives

To establish the prevalence of withdrawal of treatment macroprolactinomas and evaluate criteria prolactinoma cure medical treatment and analysing the possible factors involved.

Methods

Retrospective study of 77 patients diagnosed and treated for prolactinoma in the Sevedo Endocrinology Hospital of Asturias, from 1982 to 2012. Only 56 patients were treated exclusively with dopamine agonists and the rest were excluded. Of these 40 patients continue with treatment and 16 patients were withdrawn from treatment (eight men and eight women) after verifying the suppression of prolactin (PRL) levels and the disappearance of the pituitary mass. In 28.6% of removal and 44.6% could meet criteria.

Results

The withdrawal of treatment was on average after 11.01 ± 7.36±anos (2.26–26.8) normalization of prolactin. After removal medical treatment was resumed in 50% patients at 1, 6, 12, and 60 months respectively. The cause of restarting treatment was in all the elevation of plasma PRL levels. No significant differences between withdrawal and not withdrawn for age, sex, prolactin levels presuspension, initial tumour size, type of response, and dose of agonist withdrawal.

Conclusions

Following the withdrawal of treatment with dopamine agonists after an average of 10 years under normal PRL and almost complete tumour shrinkage was reintroduce 50% of the patients in our series. Re-introduction why treatment was in all cases prolactin elevation. No tumour regrowth in any of the control images. We observed no relation to either the initial size nor PRL figures presuspension or other predictors by the limited sample size.

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**EP822**

The effect of gonadotropin treatment on insulin resistance and cardiovascular risk factors in patients with idiopathic hypogonadotropic hypogonadism

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Introduction

Idiopathic hypogonadotropic hypogonadism (HH) is a rare disorder characterised by delayed or absent sexual maturation and infertility associated with inappropriately low gonadotropin and sex steroid levels. Insulin resistance (IR) is defined as an impaired biologic response to both endogenous and exogenous insulin. IR is a common precursor to the development of glucose intolerance, including diabetes, hypertension, and cardiovascular disease. Dyslipidaemia, apolipoprotein B-100 (ApoB-100), homocysteine, ApoA1, and high sensitive C-reactive protein (hsCRP) are another risk factors on coronary artery disease.

We aimed to to look at the role of gonadotropin replacement treatment in development of IR and other cardiovascular risk factors in patients with IHH.

Materials and methods

Twenty-four male patients with untreated IHH were enrolled into the study. IR was calculated by the homeostasis model assessment of IR (HOMA-IR) form. Plasma glucose, insulin, hsCRP, homocysteine, ApoA1, ApoB-100, LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-K), triglyceride (TG), total cholesterol (TC) levels were measured in fasting blood samples, and biochemical and hormonal analyses were performed for all study participants before and after treatment.

Results

Before and after gonadotropin replacement, HOMA-IR were 3.12 ± 1.44 and 1.98 ± 1.48; LDL-C levels were 110.4 ± 33.7 and 91.8 ± 27.6 mg/dl respectively. There was a statistically significant difference between HOMA-IR (P = 0.001) and LDL-C levels (P = 0.004). However, there was no statistically significant differences among other parameters (P > 0.05).

Conclusions

Gonadotropin replacement can significantly improve patients’ insulin sensitivity and decrease serum LDL-C levels. Therefore, gonadotropin replacement may prevent developing diabetes mellitus and cardiovascular diseases in future.

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**EP823**

Clinical features and treatment outcomes of resistant acromegaly patients: a single-centre study

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Introduction

Disease control in acromegaly can be achieved by surgery, medical treatment, and radiotherapy either alone or in combination. The acromegaly patients whom tumour shrinkage cannot be provided or growth hormone levels do not decrease under multiple treatment modalities are designated as resistant acromegaly. We aimed in our study to evaluate the clinical features of resistant acromegaly patients and determine their responses to different treatment modalities.

Methods and results

47 acromegaly patients were enrolled between 2007 and 2015 in this study. 18 of patients (ten men and eight women) were accepted as resistant acromegaly according to their clinical course. The median age, median tumour size and mean IGF1 levels at diagnosis were found 36.5 (28–62), 21 mm (12–70), and 1184 ± 567 ng/ml respectively. The mean numbers of their operation and radiation were found 2 (0–3) and 1 (0–1). Of these 18 procedures, 15 were transphenoidal procedures and three involved transfrontal surgery. Histological evaluation revealed exhibition of sparse granular staining in eight patients. Long acting somatostatin analogue therapy dose was increased in three patients. Cabergoline (0.5–2 mg/week) and pegvisomant therapy were added to their somatostatin analogue therapy in five and ten patients respectively. The mean follow-up was 18.4 ± 10 months. There were no difference found between these tree treatment modalities. IGF1 normalisation was achieved overall in 94% of resistant acromegaly patients.

Discussion

Resistance to traditional treatment options in acromegaly represents 25% of whole cases. We found a similar ratio as 39% in our case series. Resistant group was found to be diagnosed at younger age, with greater dimensions of tumour and found to have more sparse granular staining compatible with literature. We could not find any differences between IGF1 levels. It is also a debate as whether which treatment option is suitable for resistant patients.

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**EP824**

A rare case of GH deficiency: mucolipidoses type II/III

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Introduction

Disease control in acromegaly can be achieved by surgery, medical treatment, and radiotherapy either alone or in combination. The acromegaly patients whom tumour shrinkage cannot be provided or growth hormone levels do not decrease under multiple treatment modalities are designated as resistant acromegaly. We aimed in our study to evaluate the clinical features of resistant acromegaly patients and determine their responses to different treatment modalities.

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Discussion

Resistance to traditional treatment options in acromegaly represents 25% of whole cases. We found a similar ratio as 39% in our case series. Resistant group was found to be diagnosed at younger age, with greater dimensions of tumour and found to have more sparse granular staining compatible with literature. We could not find any differences between IGF1 levels. It is also a debate as whether which treatment option is suitable for resistant patients.

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Introduction
Mucolipidoses II/III (ML) are rare autosomal recessive lysosomal storage disorders (incidence: 1/325 000 live births). They have overlapping clinical phenotypes with mucopolysaccharidosis disorders and include growth retardation, facial dysmorphism, skeletal abnormalities, respiratory and heart diseases, hepatosplenomegaly and abdominal hernias. There is no specific treatment and the management has been limited to supportive care.

Case presentation
A Malnolache aged 18, boy of an young non-consanguineous apparently healthy couple, in evidence of the Genetics Department for mucopolysaccharidosis type I, was first addressed to the Endocrinology Department at the age of 14 years 4 months for investigations of growth retardation. The clinical examination revealed short stature (−4.5 s.d.), ‘elf’ facies, limited extension and abduction of the upper limbs with bilateral tendon retraction of the fingers and also in the radiocarpal and elbow joints, decreased mobility of the spine and waddling walk with wide support base; no signs of pubertal onset. Wrist radiography revealed delayed bone age of ~6 years. Somatotropic axis investigations revealed low IGF1 (62.4 ng/ml, n=220–972). GH = 0.42 ng/ml, without stimulation at the arginine test: GH = 2.75 ng/ml predicting for GH deficiency. Since there were not known contraindications, GH replacement therapy was started with an initial dose of 0.035 mg/kg per day and biannual reassessments were performed. After 4 years of treatment the medium growth rate was 0.42 cm/month and no side effects were reported. The last wrist radiography revealed delayed bone age (11 years and 6 months) permitting treatment continuation. At the last evaluation the enzymes a-iduronidase, iduronate-2-sulfatase, arylsulfatase B, b-galactosidase could be assessed and were indicative of MLV II/III.

Conclusions
Corroborating the clinical phenotype, biological data and evolution, this case can be assessed and were indicative of MLV II/III.

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EP826
Acquired male hypogonadotropic hypogonadism in a type 2 diabetes patient revealing empty sella
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Introduction
Empty sella in male patients is a very rare situation. It could be diagnosis in acquired male hypogonadotropic hypogonadism or hypopituitarism.

Case report
A 55-year-old type 2 diabetes male was referred to our hospital with erectile dysfunction (ED). He has three children. His secondary sex characteristics, sexual function, and ejaculation were previously normal but for the last 3 years he had ED. His genital stage was Tanner V, and pubic hair stage was Tanner III. There were no varicoceles. The diabetes was poorly controlled (HbA1c = 9%). His hormonal data were LH 1.1 mIU/ml (normal: 2–8 mIU/ml), FSH 1.8 mIU/ml (2–12 mIU/ml), testosterone 1.2 ng/ml (3–7 ng/ml), and FT4 13 pmol/l (10–20 pmol/l). The rate of PSA was normal. Magnetic resonance imaging of the head revealed slight depression of the diaphragma sellae, indicating an ‘empty sella’. We diagnosed acquired hypogonadotropic hypogonadism related empty sella. A replacement androgen therapy was introduced. Twelve months after hormone replacement therapy, the ED wasn’t disappear but the quality of life of this patient was better.

Discussion
ED is common in type 2 diabetes men poorly controlled. It may reveal endocrine dysfunction. Such as acquired functional male hypogonadotropic hypogonadism (MHH). Pituitary MRI is frequently normal.

Conclusion
In this observation, we report a common situation in type 2 diabetes patients which revealed a rare case of acquired MHH due to empty sella. Pituitary MRI is interesting in acquired MHH and can reveal multiphases others endocrine deficiency.

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EP827
Early postoperative basal cortisol level as good predictor of hypothalamic–pituitary–adrenal axis function after transphenoidal surgery for pituitary tumours
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Accurate assessment of the hypothalamic–pituitary–adrenal (HPA) axis is important for the appropriate management of patients with pituitary tumours after transphenoidal surgery. The aim of our study was to evaluate the clinical relevance of the early postoperative basal cortisol level in assessing postoperative HPA axis function. We performed a retrospective analysis of 68 patients (male:female = 36:32, age 59.5 years, range 21–77) treated by transphenoidal surgery between September 2011 and October 2014 at our centre of neuroendocrinology (44 nonfunctioning pituitary adenoma, 15 somatotrophinomas, five symptomatic Rathke’s cleft cysts bigger than 15 mm, three craniopharyngeomas, and one macroprolactinoma resistant to medical therapy). Patients with Cushing’s disease were excluded as well as patients with preoperative HPA insufficiency. Early postoperative basal cortisol levels (measured on the second postoperative day) and a Synacthen stimulation test (performed 10–12 weeks after the operation with a peak cortisol level of > 550 nmol/l considered as normal response) were analyzed to assess HPA axis function during follow-up. We found that basal cortisol level of ≥ 249.5 nmol/l measured on the second day after the operation is a sensitive and accurate predictor of normal postoperative HPA axis function, with a sensitivity of 87.8%, and a specificity of 52.6%. Our data suggest that early postoperative cortisol level of ≥ 249.5 nmol/l predicts distant, normal postoperative HPA axis function following transphenoidal surgery.

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EP828
A case of adrenal crisis secondary to ipilimumab-induced autoimmune hypophysitis
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A 42-year-old man undergoing ipilimumab therapy for stage IV metastatic melanoma presented after his third dose with vomiting, abdominal pain, hypotension, and pyrexia. He was treated as a presumed line sepsis. Four days prior to admission, thyroid function test showed TSH of 7.9 nmol/l and TSH 0.02 mU/l and he was treated with levothyroxine. A pituitary profile was carried out on admission and the results were as follows, cortisol was 24 nmol/l, testosterone <0.2 nmol/l, LH 1.5 U/l, FSH 5.1 U/l, and prolactin 135 mU/l. Pituitary profile had been normal at start of treatment. Acting on the above results he was commenced on hydrocortisone and clinically improved rapidly. CT brain found no abnormality in the pituitary region. MRI showed an atrophic pituitary with homogeneous enhancement, normal stalk and a preserved posterior pituitary bright spot. Given the finding of new pan-hypopituitarism he was treated as an adrenal crisis secondary to ipilimumab related autoimmune hypophysitis, despite lack of pituitary or stalk enlargement on imaging. There is no consensus in the literature on how to manage ipilimumab related hypophysitis. Some centres advocate high dose i.v. or oral steroids, while other centres feel that steroids do not affect the outcome. Our patient was treated with high dose i.v. methylprednisolone therapy followed by a rapidly reducing dose of oral prednisolone therapy. He had symptomatic improvement from this, but continues to demonstrate pan-hypopituitarism at assessment 3 months after treatment. This case describes adrenal crisis secondary to immune related hypophysitis caused by ipilimumab and management of it with i.v. methylprednisolone. Frequency of immunotherapy for treating solid organ tumours is increasing and clinicians need to be aware of these life threatening side effects and their treatment.

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EP829
Glucose homeostasis alterations in Cushing’s disease: epidemiology, anthropometric assessment and the role of family history of type 2 diabetes
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Introduction
Cushing’s disease (CD) leads to glucose homeostasis alterations, obesity, unfavorable changes in body composition and cardiovascular complications.

Aim of study
i) Prospective evaluation of the frequency of pre-diabetes and diabetes.

ii) Assessment of insulin resistance (IR) indices in CD.

iii) Analysis of the influence of family history of type 2 diabetes (T2D) on the anthropometry in CD.

Methods
The study group included 47 patients with CD (37 women and ten men, aged 43.1 ±14.6). Waist and hip circumferences, BMI, and body fat content were recorded. Glucose and insulin levels during an oral glucose tolerance test (OGTT) were assessed. HOMA-IR, QUICKI, and Matsuda indices were calculated. Patients previously diagnosed with diabetes were examined exclusively for fasting glucose and HbA1c.

Results
Sixteen patients (34%) had diabetes, another 18 (38.3%) had pre-diabetes. Hypertension was confirmed in 37 patients (78.7%). Mean total fat content was 34.52 ±10.64 kg and trunk fat was 17.49 ±5.18 kg. Mean BMI was 30.9 ±6.6 kg/m². Obesity was confirmed in 23 patients (48.9%) and overweight in 17 (36.2%). In patients with hypertension trunk fat was higher than in the normotensive group (18.38 ±2.47 kg vs 14.25 ±5.2 kg, P < 0.05). Positive family history of T2D was found in 15 patients (32%). It was associated with a greater hip circumference (114.37 ±17.84 cm vs 102.81 ±9.6 cm, P < 0.05) compared to those without T2D in the family history. Matsuda and QUICKI indices were higher in patients without concomitant glucose homeostasis alterations than in

patients with pre-diabetes (4.01 ±2.04 vs 2.08 ±0.92, P = 0.001 and 0.338 ± 0.034 vs 0.311 ±0.024, P = 0.01 respectively). There was no significant difference with regards to HOMA-IR (2.78 ±1.44 vs 5.33 ±4.82, P = 0.08).

Conclusions
i) Glucose homeostasis alterations were observed in 70% of patients with CD.

ii) We confirmed the association between the presence of arterial hypertension and trunk fat content. iii) The family history of T2D may be associated with a higher risk of obesity in CD. iv) Matsuda index contrary to HOMA-IR may be a more sensitive marker of IR in CD.

Disclosure
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EP830
Cushing’s disease: reversibility of glucose homeostasis alterations and improvement in insulin resistance indices following a successful, transphenoidal surgery
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Aim of study
i) To assess the reversibility of glucose homeostasis alterations and dynamics of inflammatory and coagulation parameters after the successful transphenoidal surgery (TSS) for CD, ii) Analysis of the early improvement in insulin resistance (IR) indices following TSS.

Methods
The group consisted of 26 patients (22 women and four men; aged 41.5 ±13.3) with early remission of CD. Anthropometric parameters, glucose, and insulin levels during an oral glucose tolerance test (OGTT), HbA1c, hsCRP, fibrinogen, and D-dimers were assessed prior to, and 3 months after TSS. HOMA-IR, QUICKI, and Matsuda indices were calculated. Patients previously diagnosed with diabetes were assessed exclusively for fasting glucose and HbA1c.

Results
Four patients (15.4%) had been diagnosed with diabetes prior to CD confirmation. Five patients (19.2%) were diagnosed with diabetes based on OGTT results prior to surgery. Ten patients (38.5%) were diagnosed with impaired glucose tolerance. A significant decrease in OGTT parameters was confirmed: fasting blood glucose (95.9 ±17.4 mg/dl vs 83.8 ±13.4 mg/dl, P < 0.05), mean blood glucose (155.4 ±34.1 mg/dl vs 117.3 ±21.6 mg/dl, P < 0.0001), 60-min glucose (182.6 ±45 mg/dl vs 135.8 ±30.6 mg/dl, P < 0.001), and 120-min glucose (161.5 ±52.2 mg/dl vs 118.7 ±33.9 mg/dl, P < 0.05). The Matsuda index and QUICKI improved significantly (2.8 ±1.8 vs 5.2 ±3.6, P < 0.01 and 0.33 ±0.03 vs 0.35 ±0.04, P < 0.05 respectively). Three months after TSS decrease in BMI and reduction in waist and hip circumference were not significant. No differences were observed with regards to mean, fasting and 120-min insulin levels, HbA1c, HOMA-IR, hsCRP, D-dimers, and fibrinogen.

Conclusions
i) Three months following successful TSS for CD significant decrease in fasting, mean and 120-min OGTT glucose levels could already be seen. ii) The Matsuda index and QUICKI might be more sensitive IR indices in the early postoperative period compared to commonly used HOMA-IR. iii) To demonstrate improvement in anthropometric parameters, insulin levels during OGTT, inflammatory and coagulation parameters, a longer follow-up may be required.

Disclosure
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EP831

Post-operative ACTH and cortisol values and its correlation with long-term clinical features in Cushing's disease

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Introduction

It has been described that early post-operative cortisol value <2 μg/dl might predict long-term remission while ACTH value has been less described.

Objective

To study early post-operative ACTH and cortisol levels in Cushing’s disease patients as predictor factor of long-term remission.

Patients

61 consecutive patients (12 men/49 women), mean age 42.6 years (17–86 years) undergoing transphenoidal hypophysectomy for Cushing’s disease from 2005 to 2014 in our hospital. Mean follow-up period 32.1 ± 23.6 months. Post-operative ACTH and cortisol were measured, without replacement treatment, every 4–6 h. We study early clinical features, hormone values, radiological images, histological and surgical findings and clinical outcome at the end of the follow-up period.

Results

54 patients (88.5%) met clinical criteria for remission (97.3% micro, 77.7% macro, and 66.6% without MRI). Total surgical adenaoma removal was performed in 86% patients (except six partial resections and two hemi/hypophysectomy based on cathetherism result). After initial surgery, post-operative serum cortisol was undetectable (<2 μg/dl) in 40 patients (27 micro, ten macro, and three without MRI). Recurrence was observed in 12/54 (22.2%) of the patients; 19.3±12.2 months after achieving disease-remission, with a higher ACTH nadir value after surgery (25.9±15.6 pg/ml) vs 9.2±8.5 pg/ml; P = 0.005) and a long time to achieve cortisol nadir <2 μg/dl (58.9±24.4 months vs 40±20.6 months; P = 0.044), while there were not differences in cortisol nadir value, adenoma size, sex, and age between recurrence and remission patients.

Conclusions

Intraoperative identification and selective removal of the pituitary adenoma, even if they were not identified by preoperative MRI, correlated with initial clinical remission in our patients. Early post-operative cortisol and ACTH measurements (without hormonal therapy replacement) have a prognostic value. Cortisol level <2 μg/dl has a curative predictive value in patients with Cushing’s disease while a higher ACTH value after surgery and a long time to achieve cortisol nadir can predict recurrence.

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EP832

Who needs pre-operative medical blockade for Cushing’s disease?

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The definitive treatment for Cushing’s disease is curative surgery. Patients with severe disease burden will likely require pre-operative medical blockade to reduce the risk of peri- and post-operative complications. The threshold for deciding when to medically block excess cortisol is currently based on clinical judgment. Expert centres may use a different criteria to determine this. There is no widely adopted tool for evaluating the clinical severity of Cushing’s disease.

Methods

We retrospectively identified 30 consecutive patients diagnosed with Cushing’s disease who proceeded to transphenoidal surgery. Using the Sonino Cushing’s severity index (CSI) we then retrospectively calculated each patient’s clinical severity disease score by reviewing their medical notes.

Results

All 30 patients (100%) had sufficient information documented in their medical records to enable retrospective calculation of their CSI score (mean 5.8, range 0–10). Twenty-three percent (7/30) received pre-operative medical blockade. Of the seven patients who received blockade: five received metyrapone alone, one ketoconazole alone, and one received both metyrapone and ketoconazole. The mean duration of blockade was 14 weeks (range 2–30). The mean CSI of patients deemed to need pre-operative blockade was 7.9 compared to 5.2 in the patients who were deemed to not need prior optimisation (P = 0.017). Only one of 18 patients (6%) with a CSI < 7 was prescribed blockade. Six of the 12 patients (50%) with a SCI in the range ≥ 7 received medical blockade.

Conclusion

We report our recent practice which shows that patients with a CSI of < 7 are very unlikely to require pre-operative medical blockade. However, CSI of 7–9 will often be an indication for blockade and CSI of ≥ 10 is highly likely to be an indication. As such this scoring system with these associated cut off values could easily be utilised in clinical practice to guide medical decision making and facilitate comparison outcomes between expert centres.

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EP833

Sarcoidosis in a 53-year-old women followed for a refractory thyroid carcinoma: a misleading association

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Sarcoidosis is a relatively frequent systemic disease of unknown origin. Prevalence is about 4.7–64 in 100 000. We report the case of a 53-year-old woman followed in our institution since 2007 for a thyroid carcinoma. In 2010, she was diagnosed refractory thyroid carcinoma because of a high thyroglobulin assay (477 μg/l) without uptake on post-therapeutic (131I) whole body scan. Thereafter, the story is marked by the appearance in 2011 of multiple cervical and mediastinal lymph nodes, pulmonary and bones lesions. Bones lesions were treated with surgery, additive radiation therapy and cementoplasty. Between 2011 and 2013, we observed pulmonary lesions progression with an aspect of lymphangitic carcinomatosis. In early 2013, morphologic evaluation showed the appearance of multiple lymph nodes (hepatic hilum, inguinal bilaterally). Biologically, we noted a slight increase of thyroglobulin assay (711 μg/l). In May 2013, a tyrosine kinase inhibitor, Sorafenib 400 mg twice a day was started. Six months later, a therapeutic evaluation was performed. TEP–TDM showed a majoration of mediastinal, abdominal, and inguinal lymph nodes and pulmonary lesions uptakes (SUV max 12.8) and an intense splenic uptake. Biologically, thyroglobulin assay remained paradoxically stable (673 μg/l). Because of this atypical presentation for a thyroid metastasis disease (lymphangitic carcinomatosis, unusual splenic metastasis, and stable thyroglobulin assay) and past history of breast cancer, a biopsy of a left inguinal lymph node was finally performed. Histological analysis demonstrated an aspect of epitheloid cell granuloma reaction with no caseous necrosis. This aspect was consistent with the diagnosis of sarcoidosis. Sorafenib was discontinued and a corticotherapy was started, enabling an improvement of respiratory symptoms. TEP–TDM performed in April 2014 showed a disappearance of all lymph nodes, pulmonary, and splenic uptakes. In conclusion, sarcoidosis should be considered in case of atypical thyroid metastatic disease, when presentation is consistent with this diagnosis.

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EP834

What are the delays in the management of thyroid cancer?

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Introduction

This audit aims to evidence the compliance of our practice with guidelines on the management of thyroid cancer. This may help to promote quality improvement in areas where there is substandard clinical care and service provision.

Method

In this retrospective study, patients diagnosed with thyroid cancers at our unit between 2009 and 2014 were identified. Electronic records were examined to establish the dates of referral, clinic attendance, investigations, and treatment, allowing us to determine whether patients received timely assessment and treatment. The quality of our ultrasound reporting and inadequacies of cytological assessment were also documented. A comparison was made against standards as proposed by the British Thyroid Association.

Results

There were 37 cases of thyroid cancer. 18 patients presented with a symptomatic thyroid nodule, five as incidental radiological findings and 14 as incidental pathological findings. Of the 23 cases with suspicious thyroid nodules, 11 were
not seen in clinic within 2 weeks of referral and eight did not have first definitive treatment within 62 days. The mean time to their diagnostic fine-needle aspiration (FNA) was 32 days. Of the 30 ultrasound scans completed, 23 were performed prior to Endocrine Clinic. However, none of these reports included all suggested features for risk stratifying thyroid nodules. Of the 41 FNA performed, 12 yielded inadequate specimens. The mean time to a repeat FNA was 104 days.

Conclusion

There was a considerable proportion of inadequate FNA specimens and thyroid nodules were poorly classified on ultrasound reporting. This may be why there was a significant lag period to a diagnostic FNA with subsequent delays to management. We recommend ultrasound assessment for risk stratification of all thyroid nodules and that this is clearly reported. In addition, any inadequate specimens should have a repeat FNA urgently under ultrasound guidance.

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EP835

Ectopic ACTH secretion by metastatic medullary thyroid carcinoma

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A 45-year-old male known case of sporadic medullary thyroid carcinoma with metastasis to lymph nodes and bone. He underwent total thyroidectomy and modified neck dissection and external radiation in 2003. He was admitted with MTC which was progressive with rising calcitonin from 9000 to 40 000 pg/l. He underwent urgent tracheotomy and assessed by ENT and found to have bilateral vocal cord palsy. Patient improved; however on further assessment he was found to have severe proximal muscle weakness and he is unable to stand from sitting position.

Hormonal assay

<table>
<thead>
<tr>
<th>Patient</th>
<th>ACTH</th>
<th>Serum cortisol (am)</th>
<th>Serum cortisol (pm)</th>
<th>24 h U for free cortisol</th>
<th>Dexamethasone suppression test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>61 pg/ml</td>
<td>1089 nmol/l</td>
<td>1004 nmol/l</td>
<td>562 nmol/l</td>
<td>No suppression</td>
</tr>
</tbody>
</table>

Radiological investigations

Pituitary MRI is normal. MRI spine thoracic show multiple bony mets with no cord compression. Bilateral inferior petrosal sinus sampling (IPSS) for ACTH levels. CRH + vasopressin stimulation: ACTH 117 – max response 127 nmol/ cortisol 1003 – max response 1045 nmol/l.

Discussion

The diagnosis is ACTH-dependant Cushing’s syndrome. The most likely the underlying cause of this condition in this patient is due to ectopic ACTH secretion by metastatic medullary thyroid carcinoma.

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EP837

Comparable ablation outcome between second and third ablation doses of 30 mCi radioactive iodine (131I) in patients with papillary thyroid cancer

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Introduction

Complete ablation of residual thyroid tissue in patients with papillary thyroid cancer decreases locoregional recurrence, distant metastases and cancer death. No single group achieved 100% complete ablation post first ablation dose with variable successful complete ablation rate. In patients who failed to achieve complete ablation a reablation dose is recommended to have complete ablation outcome. Post second ablation dose some patients still have small residual thyroid tissue in the neck, that warrants small third ablation dose of 131I to achieve complete ablation.

Aim

The aim of the current study is to compare ablation outcome post 30 mCi ablation dose of 131I used as a second and as a third ablation dose.

Patients and methods

Retrospective analysis of data of 372 patients with papillary thyroid cancer confined to the thyroid gland referred post total thyroidectomy for 131I ablation was performed. All received first ablation dose of 100 mCi of 131I. Presence of residual thyroid tissue in follow-up 131I whole body scan (WBS) with elevated unsuppressed serum thyroglobulin (Tg) level indicate incomplete ablation outcome. Those patients received 30 mCi of 131I reablation on outpatient basis. Patients post second ablation dose with small residual thyroid tissue in the neck seen in follow-up 131I WBS 6–9 months post second ablation dose with elevated serum Tg level received a third ablation dose of 30 mCi. Follow-up WBS and Tg level were performed 6–9 months post third dose to assess ablation outcome.

Results

Complete ablation rate post first dose was reported in 249 patients (66.9%). Out of the remaining 123 patients complete ablation was achieved post 30 mCi second ablation dose in 89 patients (72.4%) with an overall complete ablation post two doses achieved in 338 patients (90.9%). A third ablation dose of 30 mCi was given to the remaining 34 patients. Complete ablation was reported in 26 patients (76.5%), with statistically insignificant difference (P = 0.05) between complete ablation outcome using 30 mCi as a second or as a third ablation dose. Successful complete ablation post three doses of 131I (total dose of 160 mCi) was achieved in 364 patients (97.8%).

Conclusion

Complete ablation outcome rate between second and third ablation doses of 30 mCi of 131I are comparable with no statistically significant difference.

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EP838
Well-differentiated thyroid cancer: the Philippine General Hospital experience
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Well-differentiated thyroid carcinoma (WDTC) is the most common thyroid malignancy. Although, associated with good prognosis, it may have a highly recurrent and fatal outcome in selected groups of patients. Filipinos in particular were reported to be the ethnic group with the highest incidence of thyroid cancer in several studies. Thyroid cancer among Filipinos were also observed to be more aggressive and recurrent in nature. This paper aims to describe the experience of a Philippine Tertiary Care Centre in managing patients with differentiated thyroid cancer. This is a retrospective cohort study of 723 patients diagnosed with WDTC (649 papillary and 79 follicular). We evaluated clinic–pathologic profile, ultrasound features, management received, clinical course, tumour recurrence, and eventual outcome during a mean follow-up period of 5 years. Mean age at presentation was 43 ±13 for papillary thyroid cancer (PTC) and 44±13 for follicular thyroid cancer (FTC). Majority of both FTC (63.2%) and PTC (54.4%) presented initially as stage I. Greater FTC cases (12.7% vs 3.7%) presented with distant metastases with lung and bone being the most common. Nodal metastases at presentation were frequent among PTC (29.9% vs 7.6%). Majority of cases received total thyroidectomy, subsequent radioactive iodine therapy and TSH suppression therapy which led to disease free state. Excluding patients with distant metastases at presentation, recurrence rates for papillary and follicular thyroid cancer were 30.1 and 18.8% respectively. Recurrences for PTC and FTC frequently occurred within 15–16 months from the initial post-surgical radioactive iodine therapy. PTC among Filipinos presents at a younger age, larger tumour size, higher distant metastases at presentation and a higher recurrence rate suggesting a more aggressive and recurrent behaviour for this type of thyroid malignancy. FTC among Filipinos also presents at a younger age and a higher recurrence rate but appears to behave similarly with other racial groups.
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EP839
Risk factors for recurrence in Filipinos with well-differentiated thyroid cancer
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The incidence of recurrent well-differentiated thyroid cancer (WDTC) continues to rise as better imaging test and more sensitive monitoring improves disease surveillance. Despite its excellent prognosis, increasing morbidity from recurrent diseases continues to affect long-term outcome of most patients leading to higher medical cost and poorer quality of life. Filipino ethnicity in particular was reported to have the highest incidence of thyroid cancer with a highly aggressive and recurrent nature. This paper aims to identify associated risk factors for recurrence among Filipinos with WDTC. This is a retrospective cohort study of 723 patients diagnosed with WDTC seen at Philippine General Hospital (PGH). Study population was divided into three groups based on presence or absence of recurrence. Recurrence was considered if the patient had clinical, biochemical or radiologic evidence of cancer remnants after surgery. Multivariable logistic regression analyses were used to determine significant predictors of recurrence. 214 (32.9%) patients with papillary thyroid cancer (PTC) and 23 (29.1%) patients with follicular thyroid cancer (FTC) developed recurrence within a median interval of 13 months and 26 months from thyroidectomy respectively. Age >45 (HR = 1.44), multifocality of cancer (HR = 1.43), nodal involvement (HR = 4.0) and distant metastases at presentation (HR = 2.78) were the risk factors identified to negatively impact the risk of recurrence for PTC. Follicular variant histology (HR = 0.60) and post-surgical radioactive iodine ablation therapy (HR = 0.31) were protective factors for PTC recurrence. Distant metastases at presentation (HR = 19.4) and post-surgical radioactive iodine ablation therapy (HR=0.41) were identified for FTC recurrence. Lymph node metastases at presentation was the most important predictor of recurrence in PTC while it was distant metastases at presentation for FTC recurrence. Identified recurrence factors for WDTC among Filipinos in this study will be helpful in guiding the intensity of their treatment strategies and long-term thyroid cancer surveillance aimed to reduce future morbidity and mortality.
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EP840
Follicular variant of papillary thyroid carcinoma: an intermediate clinical entity
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Follicular variant papillary thyroid cancer (FV-PTC) appeared to be the most common subtype representing between 9 and 22.5% of all PTC cases. With the dramatic increase in thyroid cancer incidence, FV-PTC has also been increasingly diagnosed in recent times. Despite its high incidence, the clinical behaviour, prognosis and outcome of FV-PTC remains controversial and challenging for most physicians. This study aims to compare the disease characteristics of FV-PTC with Classic-PTC and FTC in a single institution in the Philippines. This is a retrospective cohort study of 606 thyroid cancer patients diagnosed as C-PTC (n = 440), FV-PTC (n = 87) or FTC (n = 79) by biopsy. Different clinical variables of three groups were then compared using a univariate logistic regression analysis. FV-PTC and C-PTC presented similarly with higher rates of multifocality (25.3% and 22.7% vs 7.6%) and bilateral involvement (20.7% and 17.1% vs 6.3%) as compared to FTC. C-PTC (37.7%) presented with high nodal involvement at presentation while both FV-PTC (8.1%) and FTC (7.6%) presented with less nodal metastases. Distant metastases was observed highest among the FTC (12.7%) group followed by FV-PTC (5.8%) and rarely in C-PTC (3.4%). Majority of patients underwent complete thyroidectomy and post-surgical radioactive iodine ablative therapy with similar rates across the groups. Recurrence rate was observed to be highest among C-PTC (39.4%) while FV-PTC (18.4%) had the lowest recurrence rate. FV-PTC resulted in almost 50% reduction (HR = 0.4954; P value = 0.007) in recurrence risk as compared with C-PTC. Mortality rate was highest among FTC (2.5%) group while FV-PTC (0%) and C-PTC (0.5%) had a similarly low mortality rate. FV-PTC represents a major sub-type of PTC that represents an intermediate entity between C-PTC and FTC. Although it behaves clinically like FTC presenting with lower lymph node metastases and higher distant metastases than C-PTC, its long-term survival and prognosis is quite similar with that of C-PTC. Treatment recommendations for C-PTC and FTC can be applied to FV-PTC cases.
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EP841
FNAC and frozen section correlation with definitive histology in thyroid diseases
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Introduction
The ability to diagnose thyroid cancers pre-op or intra-operatively by Fine needle aspiration cytology (FNAC) or frozen section (FS) leads to the delivery of appropriate one stage surgical management. We aim to study the concordance and discordance of FNAC and FS with final histology in thyroid pathologies.

Methods
All thyroid procedures from 2007 to 2011 (n = 423), involving FNAC and or Frozen Section (FS) in their management pathway were included. FNAC (n = 159) were classified in a five tier system (non-diagnostic, benign, atypical, suspicious or malignant). FS (n = 128) were classified as inconclusive, benign, suspicious or malignant. FNAC and FS were correlated with final histopathology.

Results
Out of 159 FNAC 72 (40.8%). PPV 92.8%) showed correlation with final histology, 61 (38.3%) were reported undetermined as Atypical (n = 23), follicular neoplasms (n = 27) or suspicious for malignancy (n = 11). Within 61 undetermined FNAC there were 25 malignancies (40.6%) detected in final histology. Frozen sections; 104 out of 128 showed correlation (81.2%. PPV 99.0%). 15 false negative and one false positive FS were noted. Out of six suspicious FS; four showed benign pathology and two showed malignancies. There were two inconclusive FS showed malignancies in histology.

Conclusion
In conclusion, until now FNAC is considered as the best modality to triage the thyroid nodule pre-operatively. Atypical and follicular neoplasm cytology categories warrants further clinical assessment and close follow ups when appear benign. The intra operative frozen sections are helpful to perform a one stage operation for suspicious thyroid lesion. This study also highlights the recognised limitation of intra operative frozen section analysis of thyroid neoplasia.
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Endocrine Abstracts (2015) Vol 37
Clinical features, demographic, staging and prognostic factors in patients with microcarcinoma papillary thyroid
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Introduction
Papillary microcarcinomas tiroides (MCT) are tumours less than or equal to centimeter size, mostly indetectables in the clinic and found incidentally after a thyroidectomy performed for another reason, management is under discussion and its prevalence is increased ~30%, it is believed that the increased use of thyroid ultrasound.

Review
16 patients with MCT in a province of southern Spain and evaluate the clinical and prognostic variables of our patients. Mostly women 15/1, age 44–74 years X 50. Most MCT found are incidental finding in Total thyroidectomy (TT) euthyroid BSM 13/16, other causes of surgery: Graves’ disease 1/16 and 1/16 parathyroid adenoma. Hyperthyroidism 2/1. Histologically since, given the size average 4.4 mm, only one case of multifocality without capsular most or vascular invasion. In two cases has been extended thyroidectomy were no outbreaks of MCT. The capsular invasion and follicular variety associated with increased vigilance in our patients. They have only received 2/16 I131, the most aggressive. In terms of gender, our only case man is what has been presented with worse prognosis and clinical aggressiveness from the start. Our series is small, the follow-up time is short, but data obtained corroborate published prognostic factors, the most important gender, multifocality and lymphadenopathy. 2. The heterogenity of this tumour requires us to individualise the approach, and close monitoring based on prognostic factors, to indicate the different strategies.

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Clinical significance of BRAF (V600E) mutation in papillary thyroid microcarcinoma
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Objective
The purpose of this retrospective study was to correlate BRAF (V600E) mutation with clinicopathological characteristics in papillary thyroid microcarcinoma (PTMC).

Methods
We reviewed the clinical records of patients who were operated for a papillary thyroid microcarcinoma (PTMC) between May 2011 and October 2012 in Inje University Haeundae Paik Hospital. We investigated the prevalence of the BRAF (V600E) mutation and relations between the presence of BRAF (V600E) mutation and clinicopathological characteristics in papillary thyroid microcarcinoma.

Results
Total 137 patients were included; 121 (88.3%) were female and 16 (11.7%) were male patients, aged from 22 to 74 years (mean age, 46.4 years). Median tumour size was 0.56 cm, ranging from 0.10 to 0.95 cm. The BRAF (V600E) mutation was identified in 82 patients (59.9%). Sixty patients (43.8%) had capsular invasion and 32 (23.4%) presented with some kind of extrathyroidal invasion of the tumour. Thirty-six patients had lymph node metastases. 32 (23.4%) to the central neck and 4 (2.9%) to the lateral neck. Three of four patients (75%) with lateral neck node metastases had BRAF (V600E) mutation, although this was not statistically significant. No statistically significant association was found between the BRAF (V600E) mutation and clinicopathological characteristics (age, sex, tumour size, multiplicity, lymph node status and extrathyroid tissue invasion).

Conclusion
There was no significant association between the BRAF (V600E) mutation and any of the clinicopathological characteristics. However, we have noted that the prevalence of lateral neck node metastases was more frequent in patients with BRAF (V600E) mutation than those with WT BRAF, but this trend was not statistically significant.

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Folllicular and papillary carcinoma in a subject with Graves’ disease having aggravated orbitopathy following remnant ablation
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Introduction
The risk for thyroid malignancy is higher in subjects with Graves’ disease particularly papillary thyroid cancer (PTC). However, coincidence of both PTC and follicular thyroid cancer (FTC) in these subjects is rare. In this case report we present a subject with Graves’ disease with a pathological diagnosis of PTC and FTC having aggravated orbitopathy following remnant ablation.

Case report
A 53-year-old subject was referred to our Endocrinology outpatient clinic with symptoms of retro bulbar pain and having TSH levels <0.05 (0.25–5.0 µIU/l) and FT4 67.3 pmol/l (10.6–19.4). The TSH receptor antibody level was 44 U/l (>9 (+)). She was negative for thyroglobulin and thyroid peroxidase antibodies.

The thyroid ultrasound was reported as being compatible with thyroiditis with no visible thyroid nodule. Methimazole was initiated. 2 months after initiation of the anti-thyroid drug her eye pain increased in intensity and periorbital edema occurred. Total thyroidectomy was decided as the treatment option and early postoperatively her eye symptoms resolved. The pathology report was surprising. It was compatible with a 3 cm follicular carcinoma and a 3 mm papillary carcinoma follicular variant in the left lobe together with lymphocytic thyroiditis despite the ultrasound revealing no visible nodule. She received 100 mCi radioactive iodine for remnant ablation and glucocorticoid prophylaxis therapy was initiated. The patient lost contact and did not comply with the glucocorticoid treatment. 3 months after the radiiodine the patient admitted with diplopia, bilateral exopthalmos, chemosis, periorbital edema, spontaneous retro bulbar pain and pain on down gaze. Orbita MRI revealed bilateral thickening in the superior and lateral rectus muscles. She recently received pulse glucocorticoids therapy (7 gm in 10 weeks) and will receive orbital radiotherapy.

Discussion
Although occult microPTC is frequently observed in the thyroidectomy material of subjects with Graves’ disease, it was surprising to visualize a 3 cm tumor pathologically but not radiologically. This could be explained by the very heterogeneous parenchyma masking the tumor. Aggravation of orbitopathy can be observed following remnant ablation for thyroid cancer in these subjects and glucocorticoid prophylaxis should be considered.

DOI: 10.1530/endoabs.37.EP844

Malignancy risk of thyroid nodules with repeated ‘atypia of undetermined significance/follicular lesion of undetermined significance’ diagnosis
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Introduction
‘Atypia of undetermined significance/follicular lesion of undetermined significance’ (AUS/FLUS) is a heterogeneous diagnostic thyroid fine needle aspiration biopsy (FNAB) category. AUS/FLUS is comprised of cases that cannot be definitively diagnosed as benign, suspicious for/consistent with neoplasm, suspicious for malignancy or malignant. The recommended management strategy for these cases is to perform a repeat FNAB after an appropriate time course. Although the estimated risk of malignancy for AUS/FLUS is reported 5–15%, there is growing evidence in the literature that suggest higher incidence of malignancy for this category. The purpose of this study is to estimate the malignancy risk of repeated AUS/FLUS diagnosis of thyroid fine needle aspiration biopsies.

Methods
We report retrospective analyses of 56 cases with repeated AUS/FLUS diagnosis among 5396 thyroid FNABs. The demographic data and histologic follow-up were evaluated in the study. Histological outcome was categorised as benign, malignant or well-differentiated tumors of uncertain malignant potential (WDT-UMP).

Results
Initial AUS/FLUS diagnosis was 5.2% of our FNAB series. Among these 63 (22%) of were diagnosed again as AUS/FLUS on repeated FNAB. Seven patients were lost during follow-up. Among 56 cases with a repeated diagnosis of
Association of calcium-stimulated calcitonin values with pathological findings following total thyroidectomy

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Background and objectives
Medullary thyroid carcinoma (MTC) originates from thyroid C-cells and is a calcitonin (CT) secreting tumour with aggressive behaviour. Surgery is recommended in all patients with basal or calcium-stimulated CT values of 100 pg/ml or higher due to the high probability of MTC. The objective of this study was to investigate the utility of calcium stimulation test for CT in order to distinguish MTC from C-cell Hyperplasia (CCH) preoperatively and to examine the histological findings of thyroidecomy in patients with peak stimulated CT > 100 pg/ml.

Patients and methods
A total of 52 patients with thyroid nodules and basal CT levels between 6 and 100 ng/l had a positive calcium stimulation test (peak CT > 100 ng/l) and underwent total thyroidectomy.

Results
Patients (35%) were diagnosed with MTC and 34 (65%) with CCH. 20 patients (38%) had a differentiated carcinoma of follicular origin (DTC) coexistent with either MTC or CCH. Calcium-stimulated calcitonin levels > 452 ng/l had the optimal sensitivity and positive predictive value for differentiating MTC from CCH.

Conclusion
A large percentage of MTC may be identified by peak stimulated CT levels > 100 pg/ml preoperatively, but overlapping calcitonin levels between MTC and CCH reduce the accuracy of the test. Remarkably, many patients with peak stimulated CT levels > 100 pg/ml harbour a DTC. A probable association between C-cell disease and DTC needs further examination.

EP847

Primary thyroid lymphoma: a heterogeneous disease and presentation of two different cases

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Background
Primary thyroid lymphoma (PTL) is a rare thyroid malignancy. Nevertheless, it frequently presents diagnostic and therapeutic challenges. We describe two patients with PTL with different clinical presentation and outcome.

Patients and methods
Two female patients underwent total thyroidectomy, the first, a 67-year-old female patient, because of nodular goitre and the second, a 79-year-old female patient, because of a large, painless thyroid mass accompanied by severe obstructive symptoms of the upper respiratory and gastrointestinal track.

Results
Histology of the first patient revealed lymphocytic thyroiditis and a small focus of previously unsuspected PTL, coexistent with an occult papillary thyroid carcinoma (PTC). The PTL was an incidental finding and 2 years after thyroidectomy she is free of disease without any further treatment. Histology of the second patient confirmed the clinical suspicion of PTL and established the diagnosis of a diffuse large B-cell lymphoma. Although she underwent standard chemotherapy, she died four months later.

Conclusions
PTL may have an aggressive and lethal course on the one end of the spectrum and the other one may be quite indolent. Our two cases confirm the heterogeneous nature of PTL.

DO: 10.1530/endoabs.37.EP847
Introduction
Occurrence of follicular thyroid carcinoma (FTC) is limited almost within thyroid gland, but distant metastasis is discovered uncommonly as first presentation. We experienced a rare case about recurrent bone metastasis of FTC with unknown primary site.
Case report
A 58-year-old woman complained about back pain for 3 years. A 5 cm sized mass in right 8th posterior rib was discovered and performed resection. The result of pathology was bone metastasis of FTC. Thirty four years ago, she underwent right thyroidectomy because of benign nodule. Thyroid USG shows no specific findings on remained left lobe of thyroid gland, but PET-CT presents increased uptake in the left thyroid gland, bilateral hilar and mediastinal regions, and right 8th rib. Left thyroid gland was removed totally, but primary FTC wasn’t discovered in left lobe. After operation, she received radioactive iodine (RAI) ablation with 100 mCi. However, recurrent bone metastasis of right 8th posterior rib was found in PET-CT at 6 months after surgery. Repeated operation was performed for the lesion of right rib and pathological finding shows the same results as the first operation. Because of repeated bone metastasis and increased Tg level, she was ablated four times totally with 550 mCi and underwent recurrent operations for bone metastasis of right rib. One year later, metastasis of left temporal bone was found newly and removed surgically with cranioplasty. The result of pathology was a metastasis of FTC such as the previous result. Currently, the patient is followed up in the outpatient department for conservative treatment.
Conclusions
With unknown primary site, recurrent bone metastasis of FTC is a rare case and should be treated with appropriate therapy because of poor prognosis. We report a case about recurrent bone metastasis of FTC managed with repeated operation and RAI ablation.

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EP850
BRAF V600E positive papillary thyroid carcinoma is associated with suspicious ultrasound features
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Aims
To study if BRAF V600E mutation in thyroid fine needle aspiration (FNA) is associated with specific ultrasound (US) characteristics.

Patients and methods
From 2010 to 2014 we reviewed patients with thyroid nodules with the following inclusion criteria: US guided FNA of the nodule and molecular testing for BRAF V600E on the FNA. BRAF mutation was detected using fluorescence melting curve. An expert on US, blinded to the BRAF status reviewed US examinations and recorded the sonographic characteristics for each nodule. Six US characteristics were collected: margins, echogenicity, halo, nodular vascularization, calcifications and cystic or solid composition. US findings were classified into three categories: probably benign, indeterminate or suspicious. Demographic and clinical characteristics were also analysed. Univariate (χ² and student’s t-test) and multivariate analysis were carried out.

Results
Patients were studied (85, 6% women), mean age 52 years. 79 patients showed BRAF V600E mutations on FNA (29, 2%). BRAF-positive patients were younger (48.5 ± 16.0 vs 53.6 ± 16.1 years, P < 0.05) and with different gender distribution (men 21.5% vs 11.5%, P < 0.05). BRAF-positive nodules showed at least one malignant US characteristics in 89.9% vs 49.5% in BRAF-wild type nodules (P < 0.001). BRAF-positive nodules were classified as suspicious in 63.3% and as probably benign in 10.1%. BRAF-negative nodules were classified as suspicious in 24% and probably benign in 50.5% (P < 0.001). By multivariate analysis, micro-macrocalcifications (OR 3.8 95% CI 1.8–8.0, P < 0.001) and hypoecho- genicity (OR 2.7 95% CI 1.2–6.2, P < 0.005) were independently associated with the presence of BRAF V600E mutation.

Conclusion
Suspicious US characteristics are highly associated with BRAF positive FNA. Routine cervical US and molecular testing can contribute to improve preoperative risk classification of papillary thyroid cancer.

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EP851
Mixed medullary and papillary thyroid carcinoma – a case report
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Thyroid cancers are divided into two main subgroups according to their embryonic origin: papillary cancer, the most common histologic type, seen in 75–80%, and medullary cancer, seen in 5–10% (sporadic or as a component of multiple endocrine syndrome). Because of the different phenotypic characteristics of these two cancers, it’s unusual for them to present simultaneously. Since 1980, only a few cases of simultaneous papillary and medullary thyroid cancer have been reported. Medullary thyroid cancer may have follicular or papillary components, but it’s very rare to see mixed medullary and papillary thyroid cancer in a single nodule (<2 cm). In this article, we review the characteristics of one of our patients with mixed medullary and papillary thyroid cancer. A 59-year-old woman with a history of autoimmune hepatitis and primary biliary cirrhosis, was evaluated for a 16×12 mm thyroid nodule in her right lobe. Finding medullary carcinoma by fine needle biopsy, she underwent total thyroidectomy with central lymph node dissection. Histopathologic examination of the tissues revealed ‘thyroid medullary carcinoma fields meshed with papillary carcinoma sections’. Both medullary and papillary carcinoma components were confirmed immunohistochemically. The main component of the mixed tumour was medullary carcinoma. The patient will be followed up in our Endocrinology and Metabolism Clinic. The incidence, histopathological structures, treatment, and follow up of papillary and medullary thyroid carcinomas are different. The presence of medullary thyroid carcinoma mandates further investigation to see whether other components of MEN syndromes are present, and to evaluate other family members for similar problems. The prognosis of papillary carcinoma is better than medullary thyroid cancer. The recurrence and mortality rates of medullary cancer are higher, in direct proportion to the size of the primary lesion. Mixed thyroid carcinomas are rare and are difficult to diagnose preoperatively by fine needle biopsy alone.

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EP852
Testosterone and pituitary hormones levels in thyroid cancer males patients
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The high prevalence of thyroid cancer among the male population of Ukraine during the active reproductive age (over 25 years) makes it reasonable to study the effect of the disease on testicular function. The purpose of work was to examine the state of androgen levels and pituitary hormones in men with thyroid cancer. Design and methods

The study involved 14 male patients aged from 21 to 40 years, with thyroid cancer. The control group were 46 healthy men aged from 20 to 45 years. All patients underwent determination of serum levels of total testosterone (Tt), luteinising hormone (LH), follicle-stimulating hormone (FSH) and prolactin before surgery and one month after.

Results
The study of pituitary hormones and testosterone in surveyed patients showed that the average concentration of pituitary hormones in male patients with thyroid cancer before and after surgical treatment was not significantly different from that of the control group and were within the normal vibrations. Average levels of LH were 5.7 ± 1.2 IU/l before surgery and 6.0 ± 1.1 IU/l after (P > 0.5), and do not differ from control group (4.6 ± 0.4 IU/l). Average FSH levels were 6.5 ± 1.1 IU/l before surgery vs 5.5 ± 1.8 IU/l (P > 0.5), as well 5.3 ± 0.5 IU/l in controls. The average levels of Tt in men with thyroid cancer had trend to decrease after thyroidectomy from (16.4 ± 0.5) nmol/l to (15.6 ± 0.4) nmol/l (P = 0.05 < 0.1). However, these parameters were within normal fluctuations euhonadal men and did not differ significantly from that of the control group (19.1 ± 1.7) nmol/l.

Conclusion
These data confirm that short-term failure of the thyroid gland is not pronounced adverse effect on testicular testosterone production.

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Endocrine Abstracts (2015) Vol 37
EP853 Detection of somatic oncogene alterations in FNA samples of cold nodules and 3 years follow-up of patients in Hungary

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Cold nodules are one of the most common findings on scintigraphic examinations of the thyroid gland. About 5–10% of these nodules turn out to be histologically malignant. Our aim was to examine some somatic alterations associated with thyroid cancer in FNA samples of the thyroid. These alterations included single nucleotide mutations (BRAF, HRAS, NRAS, KRAS) and genetic translocations (RET/PTC1, RET/PTC3, PAX8ex7/PPARgamma, PAX8ex8/PPARgamma). The SNPs were tested by real-time PCR with fluorescence melting curve analysis and the rearrangements were detected by Taqman probe-based quantitative real-time PCR. We have analysed 779 consecutive FNA samples and followed up the patients 3 years long. In the examined 779 samples, we found different genetic alterations (39 BRAF, 23 NRAS, 9 HRAS, 1 KRAS mutations and 1 RET/PTC3 rearrangement). After 1 year follow-up by histology, 52 cases (6.8%) were classified as malignant, from which we identified genetic alterations only in 40 (5.1%). (specificity 93.3%, sensitivity 46.2%, negative predictive value 96.0%, positive predictive value 32.9%). In two years follow-up group (n = 504) by histology, 30 cases (6.0%) were classified as malignant, from which we identified genetic alterations in 26 (5.2%). In three years follow-up group (n = 250) by histology, 13 cases (5.2%) were classified as malignant, from which we fooged genetic alterations in 14 (5.6%). No PAX8/PPARgamma rearrangements were demonstrated in the 779 samples. These data are not in complete accordance with published information. This fact might be due to several factors including the differences in iodine supply in different geographical areas.

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EP854 Primary thyroid lymphoma: an ominous and commonly forgotten association with Hashimoto’s thyroiditis

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Introduction Primary thyroid lymphoma (PTL) is rare and constitutes 2–5% of thyroid malignancies. The risk however increases with background Hashimoto’s thyroiditis. (HT) We report a patient with HT complicated by thyroid lymphoma and did a literature review on this topic.

Case presentation A 61-years-old Chinese lady with background HT on levothyroxine presented with an enlarging goitre of 6 months duration. There was weight loss of 3–4 kg, but no fever or night sweats. Examination showed an enlarged, non-tender thyroid with an enlarging goitre of 6 months duration. There was weight loss of 3–4 kg, A 61-years-old Chinese lady with background HT on levothyroxine presented with an enlarging goitre of 6 months duration. There was weight loss of 3–4 kg, A 61-years-old Chinese lady with background HT on levothyroxine presented with an enlarging goitre of 6 months duration. There was weight loss of 3–4 kg, A 61-years-old Chinese lady with background HT on levothyroxine presented with an enlarging goitre of 6 months duration. There was weight loss of 3–4 kg, A 61-years-old Chinese lady with background HT on levothyroxine presented with an enlarging goitre of 6 months duration. There was weight loss of 3–4 kg, A 61-years-old Chinese lady with background HT on levothyroxine presented with an enlarging goitre of 6 months duration. There was weight loss of 3–4 kg, A 61-years-old Chinese lady with background HT on levothyroxine presented with an enlarging goitre of 6 months duration. There was weight loss of 3–4 kg, A 61-years-old Chinese lady with background HT on levothyroxine presented with an enlarging goitre of 6 months duration. There was weight loss of 3–4 kg.

Discussion PTL has an estimated annual incidence of two cases per million and almost all are of B-cell origin. It affects middle-aged to older individuals, predominantly women. Most are diagnosed with stage I disease and the most common histologic subtype is diffuse large B-cell lymphoma. The hallmark of developing thyroid lymphoma is 40–80 times greater in patients with chronic thyroiditis. Proposed mechanisms include prolonged antigenic stimulation in the setting of autoimmune thyroiditis leading to lymphomatous transformation or malfunction of the somatic hypermutation process, a phenomenon called aberrant somatic hypermutation process, which is regarded as a mechanism of lymphomagenesis. Treatment comprises different modalities depending on histologic subtype and stage of disease.

Conclusion The diagnosis of PTL should be considered in a rapidly growing goiter especially in the background of HT. Early detection may result in improved survival.

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EP855 Vitamin-D neutralising CYP24A1 gene expression in thyroid fine-needle aspiration biopsy samples

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Objectives We previously published the result of CYP24A1 gene expression in one hundred, solely papillary thyroid carcinoma (PTC) compared to its own tumour free control from the same patient. We report an increase in CYP24A1 gene transcription in more than half of analysed PTCs. Elevated CYP24A1 protein expression was also observed in the cancerous tissue section compared to peritumoural normal thyroid tissue. In the present study we aimed to examine CYP24A1 gene transcription in thyroid fine-needle aspiration biopsy (FNAB) specimens and follow up the patients for 2 years.

Methods The gene expression analyses of 42 thyroid FNABs were carried out by Taqman probe-based quantitative real-time RT-PCR. The somatic mutation states of BRAF, NRAS, HRAS, KRAS oncogenes as well as ELE1/RET and CCDC6/RET rearrangements were also tested. Genomic DNA and total RNA were isolated from each sample using Roche High Pure kits.

Results Eight males and 34 females participated in the study. The mean age was 51.43 years. Cytology results of 28 FNABs were benign and 14 were malignant. Within the malignant specimens 13 papillary and 1 follicular type carcinoma were recognised. Altogether, 6 BRAF (rs113488022) mutations, 1 ELE1/RET translocation were detected in the malignant FNAB samples and one benign biopsy carried HRAS (rs28933406) mutation. CYP24A1 gene expression were noticed only in five FNAB samples diagnosed with PTC. We could not determine CYP24A1 specific mRNA in the benign samples. During the follow up period we identified malignant transformation in three cases from the 28 initially cytological benign FNABs. In all of these three cases PTC were certified.

Conclusion It is well established, that CYP24A1 gene activity is elevated in various cancers including thyroid carcinoma might be to protect tumour tissue from the anti proliferative and pro-apoptotic effects of 1.25-vitamin D3. Our results show that changes of CYP24A1 gene expression have no predictive value in precancerous states of thyroid and it could not help to complete the diagnosis of FNAB cytology.

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EP856 Brain metastases of thyroid carcinoma: a report of two cases and review of the literature

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Introduction Brain metastases of thyroid carcinomas are rare (0.1–5%) according to the literature data. They generally occur in a context of metastatic spread which has a serious impact on survival. We report two cases and will review the literature data.

Observations Case 1: 57-year-old patient monitoring for papillary thyroid carcinoma in its solid form (trabecular classified T4N0M1 with lung metastases. Following a neurological symptoms of tonic-clonic type of the left arm cerebro-spinal MRI revealed a 20 mm right parietal lesion and cerebellar lesion 4 mm. The rest of the staging procedures were negative. The patient referred to the oncologist was made. Up-take scan after radioiodine therapy revealed metastases: brain, lung, bone, pancreas, liver. The histological study of parietal localization confirmed his thyroid origin. Up-take scan after radioidine therapy was positive especially in brain. thyroglobulin levels are increased to 3050 ng/ml.

Conclusion Patients with thyroid carcinoma metastatic to the brain appear to have a relatively short survival time compared with other patients with thyroid carcinoma.
although this survival time is significantly longer than that noted with other solid tumour metastases to the brain. Early detection is important and specific treatment (radioidine therapy) and standard treatments (surgery, Whole Brain Radiation Therapy) can improve their prognosis.

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EP857
Aggressive papillary thyroid cancer with rare morphological features: a case report
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Introduction
Papillary thyroid cancer (PTC) is the most frequently observed type of thyroid cancer. It usually shows favorable prognosis although some aggressive pathological subtypes have been defined. In this case report we present an aggressive form of PTC with previously non defined histological features.

Case report
At initial evaluation the subject presented with a mass in the neck. Neck ultrasonography (USG) revealed a 4.9 x 2.3 mm hypo echoic nodule in the left lobe and multiple lymphadenopathies adjacent to the left thyroid lobe being suspicious for malignancy. The nodule had irregular edges and was hyper vascular in power doppler imaging (PDI). The patient underwent total thyroidectomy and ipsilateral central lymph node dissection. The pathology report was compatible with papillary thyroid cancer (PTC) and Hashimoto’s thyroiditis. The tumour was composed of 30-35% insular, 10% Tall-Cell and 55% anaplastic cells. The tumour was 45mm in size and showed pericapsular soft tissue invasion. Immunohistochemistry was positive for Thyroglobulin, TTF-1, NSE, Pan SK. The tumour was 45mm in size and showed pericapsular soft tissue invasion. Immunohistochemistry was positive for Thyroglobulin, TTF-1, NSE, Pan SK.

Result
Although PTC generally shows favorable prognosis the histomorphological features are variable and may not suit one of the previously defined PTC subtypes. Such cases as the one defined may clinically advance like anaplastic thyroid cancer.

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EP858
The evaluation of sex hormone receptors in papillary thyroid cancer as an additional tool in the post-operative risk stratification and in the pre-gravidic counselling of women with persistent disease
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Introduction
We studied the expression of oestrogen receptor (ER) and progesterone receptor (PR) in 182 female and male patients with papillary thyroid cancer (PTC) and correlated it to clinical and molecular features. ER and PR expression was demonstrated for the first time in thyroid tumours. Indeed, almost all the ER and PR positive primary tumours analysed had negative metastatic lymph-nodes. 

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EP859
Concomitant papillary thyroid cancer and Graves’ disease: an ominous association
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Background
Papillary thyroid carcinoma (PTC) in patients with background Graves’ disease (GD) has been associated with a higher risk of post-operative tumour recurrence. We present a case and review the literature for possible explanations.

Case presentation
A 55-year-old gentleman with GD treated with carbimazole presented 1 year after initial diagnosis with a 3 cm palpable thyroid nodule. Fine needle aspiration cytology (FNAC) was suggestive for malignancy. The patient underwent total thyroidectomy and ipsilateral central lymph node dissection. The pathology report was compatible with papillary thyroid cancer (T3N0M0); size of tumour: 4.7 x 2 x 2 cm. There was no lymphovascular invasion or features of aggressive histology. He received 130 millicuries of 131-iodine and was started on high dose l-thyroxine, keeping thyroid stimulating hormone (TSH) suppressed. Thyroid-stimulating hormone receptor antibody (TRAb) levels were positive at 3.3 IU/L (NR: <1), 2 years post operatively, a follow-up neck ultrasound revealed prominent lymph nodes. FNAC was positive for malignancy. There were no distant metastases. He had neck dissection followed by RAI.

Discussion
Neoplastic cells of differentiated thyroid cancer, like normal thyroid cells, express functional receptors for TSH. Thyroid stimulating antibodies might play a role in stimulating thyroid cancer growth, invasiveness and angiogenesis by up-regulating vascular endothelial growth factor, placenta growth factor, and their receptors. The antibodies have also been shown to initiate cellular proliferation by suppressing mitochondrial reactive oxygen species levels, preventing apoptosis. Apart from that, different growth factors that probably are produced by the over-stimulated, hypervascularized thyroid could also affect the growth and metastases of thyroid cancer in patients with GD. Interleukins four and ten, locally produced in thyroid glands affected by GD, also have a strong anti-apoptotic effect on malignant thyrocytes. 

Conclusion
A high index of suspicion for tumour recurrence in patients with PTC and concomitant Graves’ disease is necessary.

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EP860
Rise in incidence of differentiated thyroid cancer in the south of Spain
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Background
Recent studies have shown that the incidence of differentiated thyroid cancer (DTC) is increasing. Objective: Evaluate the incidence of DCT in a center of the south of Spain for the last 15 years and analyse the clinical and morphological factors related to DTC.

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Anaplastic thyroid cancer is a devastating disease with median survival between 1.2 and 10 months. The disease accounts for as little as 0.9–1.6% of total thyroid cancer cases, but may account for up to half of all thyroid cancer mortality. The aim of our study is to evaluate the prognostic factors and outcomes of patients diagnosed with anaplastic thyroid cancer in Ireland and review emerging treatments for this disease.

Methods and design
A retrospective analysis of the National Cancer Registry in Ireland was undertaken, for patients with a diagnosis of anaplastic thyroid cancer between 2000 and 2010. Patient, tumour, and treatment characteristics were recorded. The Kaplan–Meier method was used to determine overall survival and factors predictive of outcome were determined by univariate and multivariate analysis by cox regression using Stata 13 software.

Results
Of a total of 64 patients, 40 were female and 24 were male. The median age was 69, and 27.5% of patients had distant metastases at diagnosis. The overall median survival was 2.3 and the 6 months, 1, 2, and 5 year overall survival was 23.4, 12.5, 6.25, and 4.69% respectively. On univariate analysis age, gender, metastases at diagnosis, surgery, radiotherapy, and multimodality treatment were statistically significant indicators of prognosis, and metastases at diagnosis remained statistically significant on multivariate analysis. A review of the 7741 patients in the literature revealed a median survival of 3.67 months.

Conclusions
The British and American Thyroid associations (BTA/ATA) have comprehensive guidelines on the management of ATC. However due to the rapidity of onset of the tumour, few patients benefit substantially from aggressive conventional treatments, and survival has not changed over a period of 40 years. Personalised therapeutic approaches based on the use of targeted therapy may be the best hope to improve treatments for patients with ATC.

DOI: 10.1530/endoabs.37.EP863
A cavernous angioma-mimicking case of solitary bone and brain metastasis of the columnar cell variant of papillary thyroid carcinoma

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Background
Thyroid carcinoma has increased annually. Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy and thought to have favourable prognosis. Distant metastases are common in lungs and bones. However, brain metastases are rare and its prognosis is unfavorable. Here we reported a case of solitary brain metastases of PTC mimicking cavernous angioma in a 76-year-old woman patient.

Results
A 76-year-old woman presented memory disturbance for 3 months. On physical examination, there was a 5 cm sized mass without tenderness in sternum. The brain magnetic resonance imaging showed a lobulated lesion with a mixed signal core surrounded by low intensity rim in right frontal lobe that was not enhanced in contrast image suitable for a cavernous angioma with haemorrhage. There was a mass with necrosis in the manubrium on chest computed tomography (CT) but no abnormality in abdomen CT. We did craniotomy for tumour removal and manubrium mass biopsy in the same day. In pathological finding, brain and manubrium revealed metastatic carcinoma consistent with primary in thyroid. For investigation of thyroid cancer, we did a neck ultrasonography and it demonstrated 1 cm sized hypoechogenic nodule with coarse calcification in the left lobe. As a result of fine needle aspiration on left thyroid nodule, pathology showed a classic PTC and BRAF mutation was positive. The patient refused thyroidectomy and expired 9 months later due to pneumonia and sepsis.

Conclusion
Brain metastases with PTC mimicking cavernous angioma is extremely rare. It makes us cautious that even small PTC could occur as distant metastasis.

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Incidental papillary thyroid carcinoma prevalence in benign multinodular goitres: data from Northern Portugal

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Introduction
Incidental papillary thyroid carcinoma (PTC) in patients undergoing thyroidectomy for benign multinodular disease is a well-recognised finding. Its true prevalence remains uncertain and shows great variability between studies, ranging from 7–25%. Our purpose was to review the prevalence of PTC in thyroid glands removed for benign nodular disease at a Northern Portuguese tertiary hospital.

Methods
From December 2012 to December 2014, the histological reports of patients treated surgically for benign nodular thyroid disease were reviewed. We excluded patients with thyroid hyperfunction and those with any suspicious cytological findings (Bethesda category ≥III). Data regarding demographics and pathological findings were retrieved.

Results
Patients were included in the analysis, with a mean age of 55 ± 15 years; 87% were females. The overall prevalence of malignancy (PTC) found was 15.8% (95% CI: 11.4–21.5%). There were no statistically differences between PTC and benign groups regarding patient’s age and gender. The pathological tumour size ranged between 1 and 55 mm (median 8 mm). Most cases of PTC were microcarcinomas (19 in 32, 59.4%), with a median diameter of 4 mm (range, 1–9 mm). In respect to macrocarcinomas (13 in 32, 40.6%), the median tumour diameter was 35 mm (range, 11–55 mm). In seven patients (22%), the tumour was multifocal and in one patient (3%) vascular invasion was documented. The most common variants of PTC found were classical and follicular with 59.4 and 37.5% respectively.

Conclusions
In our series, microscopic PTC prevalence in patients undergoing thyroid surgery for benign euthyroid disease seems to be similar to the previously described.

These high rates of pathological incidental thyroid carcinomas should be taken into account and drive appropriate diagnostic and therapeutic approaches.

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Serum Galectin-3 in papillary thyroid cancer: preliminary results

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Background
There are only few reports regarding the role of serum galectin-3 (Gal-3) as an early biochemical marker in thyroid carcinoma.

Aim
To evaluate the potential overexpression of Gal-3 in sera from patients with confirmed diagnosis of papillary thyroid carcinoma (PTC).

Patients and methods
We retrospectively investigated serum Gal-3 in 40 patients referred to the surgical department for thyroidectomy. Sera were collected before surgery. We measured sera of 40 patients (mean age 48.79 ± 14.15 years): 32 women (82.5%) and seven men (17.5%). Patients were divided in four groups, based on histopathological stage: nodular goitre, PTC1, PTC2, PTC3/4. Gal-3 was measured by Elisa (Abcam, UK): sensitivity 0.12 ng/ml, intra-assay cv 6.4%, inter-assay cv 11.4%. The study was approved by Ethics Committee of the Institute.

Results
Patients showed different PTC stages at histopathological exam, as follows: 10 PTC1, 10 PTC2 and 11 PTC3/4, respectively: nine patients were diagnosed with benign nodular goitre. We found a significant difference between cancer and non-cancer patients (median Gal-3 – 8.427 ng/ml vs 4.402 ng/ml, P < 0.019), between PTC3/4 patients and those with nodular goitre (median Gal-3 – 9.069 ng/ml vs 4.402 ng/ml, P = 0.0097), and between PTC1 and goitre patients (median Gal-3 – 8.751 ng/ml vs 4.402 ng/ml, P = 0.047). In our study, we noticed higher values vs reference ranges in nodular goitre group (mean 5.046 ± 7.811 ng/ml vs 0.54 (0–2.28) ng/ml, P < 0.0001). However, serum Gal-3 did not discriminate between different PTC stages. Intra-assay cv % in our hands was 3.57%.

Conclusion
Serum Gal-3 might be considered as an early circulating tumour marker in thyroid cancer. Our preliminary data showed no association of serum Gal-3 with tumour aggressiveness.

Disclosures
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The two tyrosine kinase inhibitors, CLM29 and CLM3, have antineoplastic activity in primary cultures from anaplastic thyroid cancer obtained from fine needle aspiration

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Anaplastic thyroid cancer (ATC) is one of the most lethal endocrine malignancy, with a mean survival of about 6 months. Until now, the most effective therapy for ATC comprises a multimodal treatment protocol, including surgery, chemother-apy (doxorubicin and cisplatin), and hyperfractionated accelerated external beam radiotherapy, with a median patient survival of 10 months. A possible increase in the effectiveness of the treatment could be achieved testing the sensitivity of ‘primary anaplastic thyroid cancer cells’ (pATC) from each subject to different drugs, in this way avoiding the administration of inactive therapeutics to these patients. Here, we tested the in vitro antineoplastic effect of the two new ‘pyrazolo (3,4-d) pyrimidine’ compounds (CLM3, CLM29) in pATC obtained both from

Role of miR-26a in follicular thyroid carcinoma

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Follicular thyroid carcinoma (FTC) is the second most common thyroid malignant epithelial tumor. It is clinically asymptomatic, usually represented by a single nodule, less often multiple, with origin from thyroid follicular epithelial cells. Despite its well-differentiated characteristics, FTC may develop distant metastases through hematogenous dissemination. The molecular alterations involved in the pathogenesis of follicular neoplasia are not completely known. Recent studies have demonstrated the importance of miRNAs, small non-coding nucleic acids that regulate gene expression at post-transcriptional level. It is well known that the expression profile of miRNAs is altered in follicular thyroid carcinoma. To date, the aftermaths of deregulated expression of miRNAs in the FTC have not been clarified. In order to investigate the molecular mechanisms involved in thyroid tumorigenesis, we evaluated the effects of miR-26a modulation in a human FTC cell line. We observed that miR-26a is significantly down-regulated in FTC-133 cells as compared to a thyroid normal cell line, NTHY-ORI. Our results demonstrated that miR-26a does not directly regulate Protein Kinase C Delta (PRKCD), a known target of this miRNA, but influences its levels. PRKCD is a regulator of caspase-mediated apoptosis, vascular endothelial growth factor (VEGF)-mediated cell proliferation and iodide uptake via sodium iodide symporter (NIS). We observed that miR-26a up-regulation increases PRKCD and NIS protein levels as well as caspase activity, but does not influence VEGF secretion. These results support the hypothesis that miR-26a may influence thyroid differentiation processes and may represent a therapeutic target for future innovative therapy in advanced radio-refractory disease.

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Chemotherapy effectiveness in the treatment of non-medullary well-differentiated thyroid cancer: a systematic and case review
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Introduction

Nowadays, use of chemotherapy in well-differentiated non medullary thyroid cancer, locally advanced stage and/or with radioiodine-refractory metastases is considered of scanty value. However, in the last 40 years was not published any phase III study nor a systematic review of its use in clinical setting.

Methods

A systematic literature search was performed in databases such as Medline and Embase, among others. Two independent reviewers analysed the articles selected full text, made a critical reading and extracted results using forms designed specifically. A qualitative synthesis of the results was performed and the accumulated data were calculated.

Results

A total of 509 references were found. Sixteen studies involving 473 patients published were included. Thirteen studies showed individual response data to treatment. Finally, 179 patients treated with different chemotherapy alone or in combination were identified. The overall response rate (RR) was 27% (0–57%), with a 4% of patients showed a complete response (CR) and clinical benefit (CB) in 60% (14–100%). Eight studies reported data response relative to histologic subtype. The RR for the 37 cases with papillary cancer was 24% (0–50%) and 32% (5% CR) (0–100%) of 56 with follicular cancer. However, data must be interpreted carefully due to the risk of bias detected. Unlike modern studies a performance status >2 was described in about 40% of patients. Five individual studies published survival data from 54 patients with advanced CDT: the median survival was estimated at 18 months (95% CI 0–37.5), with significant differences between patients treated before 2000 vs those treated later (7 months vs 41 months, P<0.00).

Conclusion

There are insufficient data to evaluate the effectiveness of chemotherapy in patients with advanced non-medullary thyroid cancer, although, it seems to have some efficacy, therefore, it could be necessary to be tested in well-designed studies vs or in combination with new therapies.

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**EP871**

Other malignancies accompanying differentiated thyroid cancer in Turkish Cypriots: a single-centre study

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Introduction

The aim of this study was to determine the frequency and types of accompanying malignancies in Turkish subjects with differentiated thyroid cancer (DTC) residing in the northern region of Cyprus.

Subjects and methods

We retrospectively analysed 357 subjects with a diagnosis of DTC in the Departments of Endocrinology and Nuclear Medicine.

Results

A total of 17 subjects (2.9%) had an accompanying second malignancy other than DTC. Sixteen were females (94.2%) and one was male (5.8%). The mean age was 46.3 years for subjects with DTC being the only malignancy and 54.76 years for those with accompanying malignancies (P < 0.05). Out of these 17 subjects 14 had classical papillary thyroid cancer (PTC), two had PTC follicular variant, and one had follicular thyroid cancer. All subjects received radioactive iodine for remnant ablation. The secondary malignancies were breast cancer in nine subjects (52.9%), endometrium cancer in two subjects (11.7%) and acute lymphoblastic leukemia, Hodkin lymphoma, lung cancer, malignant melanoma, and gastrointestinal stromal tumour in one subject each. In 11 subjects DTC developed secondarily, in five subjects DTC developed first and in one subject DTC and the other malignancy developed synchronously.

Conclusion

The rate of accompanying malignancies in DTC was 2.9%. Classical PTC was the most frequent tumour type accompanying other malignancies (82.3%). DTC was observed four times higher in female subjects compared to male subjects. The role of gender was higher in those with accompanying malignancies. The most frequently observed accompanying malignancy was breast cancer leading by far. Only five subjects had developed a malignancy after the diagnosis of DTC and 12 subjects had a diagnosed malignancy before DTC. Thus we believe the role of RAI remnant ablation for secondary malignancy development is none or minimal.

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**EP872**

Role of thyroglobulin as a predictor of the evolution of disease in differentiated thyroid cancer

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Aim

Investigate, in patients with differentiated thyroid cancer (DTC) if thyroglobulin (Tg) values, immediately before and six months post radioiodine ablation are good predictors of disease progression.

Materials and methods

Basal Tg values (Tg-B) and rhTSH stimulated Tg (Tg-S) before ablation (0) and 6 months later (6) from 142 DTC patients, with post-surgical ablation therapy between 2003 and 2009 with a follow up of 5 years, were analysed.

Results

After a 5-year follow up, 121 patients (85.2%) were free of disease (FD). 15 patients (10.6%) had evidence of disease (ED) and six had died (4.2%). A Tg-B>0.2 ng/ml was present in 39 patients (27.5%), only one (2.5%) has ED because of positive antibodies and only one (2.5%) needed retreatment. In contrast: a Tg-S>0.2 ng/ml was present in the 103 patients (72.5%), 21 patients (20.4%) had ED and 27 (26.2%) needed retreatment. A Tg-S/0.1 ng/ml was found in 34.8% only one (2.6%) was ED and only one (2.6%) required treatment. However, 65.2% of patients had these values >1 ng/ml, of which 22.5% was considered ED and 26.7% have required retreatment. At 6-month Tg-B ablation >0.2 ng/ml, 40% was ED and 46.7% required retreatment and when Tg-S/6-ablation >1 ng/ml, 56% was ED, and 67% required retreatment in 5 years follow up.

Conclusion

Tg basal value at the time of ablation has a high specificity and sensitivity for predicting disease progression. Stimulated Tg at that time does not add predictive value. At 6-month high levels of Tg value predicts evidence of disease in 5 years follow up.

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**EP873**

Clinical and biological differences between incidental and non-incidental papillary thyroid microcarcinomas

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The clinical significance and potential morbidity of papillary thyroid microcarcinomas (PTMC) is discussed. Particularly the differences between those PTMC identified postoperatively in histological examination (incidentals), and those diagnosed preoperatively (non-incidentals). We retrospectively analysed differences in clinical presentation and course after treatment in these two groups. The study population consisted of 199 patients with PTMC who underwent surgery from 2000 to 2014. Eight patients preoperatively diagnosed of lateral compartment lymph node metastasis (LNM) were excluded, as they were considered suffering a more advanced disease. We compared characteristics, and outcomes between both groups. There were 118 incidental and 73 non-incidental PTMC. Patients with Incidental PTMC were older (55.7 years vs 50.8 years; P = 0.01), had smaller tumours (43 mm vs 79 mm; P = 0.001) and lower preoperative TSH (1.87 vs 3.06; P = 0.001). Incidence of serological or histological evidence of autonomy was not different between both groups. Multifocal disease (46.8% vs 29.5%; P = 0.02) and extracapsular invasion (25.6% vs 4%; P < 0.001) were most frequently reported in non-incidental neoplasms. One hundred and sixteen out of 122 patients treated with radioiodine had at least 1 year of follow-up (62 incidentals and 54 non-incidentals). One year after radioiodine, eight incidental cases didn’t reach remission criteria (undetectable stimulated thyroglobulin and normal high-resolution cervical ecography). Three of them persisted with biochemical disease 1, 2, and 3 years passed, one patient is waiting for surgery to identified cervical adenopathy, two achieved remission after ganglion surgery plus more radioiodine and two without additional treatment. There were two non-incidental patients without remission 1 year after ablation, both without structural disease, persistent 1 and 6 years passed. There was one biochemical relapse after initial remission in the non-incidental group. In our series, incidental and non-incidental PTMC showed differences at presentation, but similar biological behavior in the follow-up after treatment. Remnant disease is more often seen in incidental carcinomas after ablation.

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**EP874**

Differentiated thyroid cancer: tendency changes from 1970 to 2012 in the southwest of Spain

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There is a specific unit specialised in treating differentiated thyroid cancer (DTC) at the Endocrinology Department from a hospital the southwest of Spain that attends patients from two different provinces. Owing to environmental pollution, one of them has higher incidence of cancer.

To evaluate the changes in the clinical presentation of DTC over time and analyse possible differences between patients from the two provinces, we designed a descriptive retrospective study, including all DTC cases admitted from January 1970 to March 2014. Quantitative variables are expressed as median (interquartile range). All the results were standardized using specific population records from the National Institute for Statistics for each time period.

Results

Total population 1289 (255 males/1034 females). Age at diagnosis: 43 years (33–55); 82.2% were papillary thyroid cancer (PTC) while 17.5% were follicular thyroid cancer (FTC). We found a progressive increase in PTC since 1970, more marked from 1996 to the present in both sexes (mainly between 21 and 65 years at diagnosis), in tumours >1 cm (T1b–T4), as well as papillary microcarcinoma, following the same trend. A similar pattern was observed in FTC. There were no differences regarding unfavourable histological subtypes. In the 1970’s, FTC and
FTC tended to be >3-4 cm and/or with extrathyroid extension, N1 and M1, in comparison with the current presentation (<4 cm, limited to the thyroid and N0 M0). In patients from the most polluted province we detected a non-significant slightly higher percentage of high-risk tumours (8.85% vs 7.55%) without any other differences.  

Conclusion  
DTC clinical presentation has shifted from high-risk tumours at diagnosis (1970’s and 1980’s) to a low-risk profile (T1-3, N0, and M0) in the last years, with a steady increase in the number of cases per year, mainly FTC. Men have a tendency to have higher risk tumours than women.

EP875  
Thyroid cytology–biopsy correlation  
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Background  
Fine-needle aspiration (FNA) biopsies are the cornerstone of preoperative evaluation of thyroid nodules, but FNA diagnostic performance has varied across different studies. We conducted a study to evaluate the effectiveness of ultrasound guided FNA in the thyroid nodule and to review the correlation between cytopathology and histopathology.

Methods  
Prospective FNAs were collected from 332 patients who underwent thyroid surgery between 2008 and 2013. The cytological sample was assessed by a single consultant pathologist and was classified as inadequate, non-neoplastic, or indeterminate. The histology were classified as non-neoplastic (benign), neoplastic (malignant). Sensitivity, specificity, positive predictive value, and negative predictive value were calculated.

Results  
The mean age was 51.65 ± 13.40 years, 279 (84%) were women. The average size of nodules was 3.35 ± 1.41 cm. Multinodular goiter presented with dominant nodule 239 (72%) patients and 93 (28%) single nodule. Cytology analysis showed 216 (66.3%) benign, 86 (26.4%) indeterminate, and 24 (7.4%) malignant. One hundred and ninety-seven (59.3%) patients underwent total thyroidectomy. From this population indeterminate cytology rate were 75 (87.2%) benign and 11 (12.6%) malignant histopathology. The FNAs had a sensitivity of 84.62%, specificity of 99.07%, positive predictive value of 91.67%, and negative predictive value 98.15%.

Conclusions  
Ultrasound-guided FNA provides important information for the diagnosis and the preoperative evaluation of thyroid nodules. The low rate of false-positive and false-negative results suggests that it might be enough for surgical planning for thyroid nodule.

EP876  
Simultaneous occurrence of different follicular neoplasms within the same thyroid gland: a retrospective study  
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Introduction  
Neoplasms of the thyroid gland are classified according to the cell that it originates and commonly they originate from follicular or parafollicular C cells. The most common differentiated thyroid cancers (DTC) are papillary and follicular carcinomas. Coexistence of two different histological types of primary follicular thyroid neoplasm is a rare condition. There are previous reports of concomitant medullary and papillary thyroid cancers. However, there is scarce data about the simultaneous two different histological types of primary follicular thyroid tumors and this is the first study on that subject.

Method  
From January 2007 to September 2014, our institutional database was reviewed for patients who underwent thyroid surgery for various indications. Medical records and cytopathology reports of those patients were examined retrospectively. Simultaneous neoplasms of follicular origin were noted.

Results  
A total of 3700 patients were operated. Histopathological examination result was benign in 2686 (73%) patients while it was malignant in 1014 (27%) patients. Among the patients with the diagnosis of DTC only 20 (1.9%) had accompanying second neoplasia within the same thyroid gland. PTC had thyroid capsule invasion in seven patients (3%) while capsule was intact in 13 (65%). In 17 (85%) patients there wasn’t vascular invasion whereas in three patients (15%) vascular invasion was detected in PTC. Second neoplasm was follicular carcinoma in ten patients, Hurthle cell carcinoma in two patients, Hurthle cell adenoma in five patients, and follicular adenoma in three patients.  

Conclusion  
Such simultaneous tumors may be part of a familial tumour syndrome or an unidentified novel gene mutation playing role in the pathogenesis of more than one type of tumor. Based on the current evidence the synchronous occurrence of those neoplasms in a given patient is likely coincidental in the literature. Further study is required using a larger patient population with standardised genetic characterisation.

EP877  
Thyroid Imaging Reporting and Data System (TIRADS) can reduce the needed number of FNA  
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The prevalence of solid thyroid nodules is very high in the general population. Appropriate selection of cases for surgery is the most important task, when evaluating nodules. The present study wants to see if the use of Thyroid Imaging Reporting and Data System (TIRADS) could decrease the number of needed FNAB procedures.

Material and method  
174 nodules evaluated by conventional ultrasound and real time elastography, with linear multifrequency probe, Hitachi Preirus Machine, Hitachi, Inc. Prospective all nodules were classified by TIRADS system: ecogeneity (risk = inhomogeneity), margins (risk = irregular margins), shape (risk = irregular shape, taller than wide), calcification (risk = micro calcifications), lymph node (risk = presence), and increased strain (color map 4, 5, increased strain ration). TIRADS 4A, 4B, and 5 cases were referred also to FNAB. All 174 cases were operated and pathology report was obtained.

Results  
Cancer was certified in 29 of the 174 operated thyroid nodules. The number of required punctions would be in 169 cases, if we consider the AACE guidelines. If we apply the TIRADS system (all 4A, 4B, and 5 TIRADS nodules) in selecting the cases for FNAB, the number would decrease significantly up to 74 nodules. The diagnostic quality of TIRADS is very high: using the ROC method, the AUC = 0.95761, confidence limit of 0.8424-0.989 (95% LCL and 95% UPL). The sensitivity and specificity in diagnostic of cancer was excellent: diagnostic sensitivity, 86.20% with high specificity, 97.24%, with the best accuracy of 95.40%.

Conclusion  
Using TIRADS system, the correct evaluation of the majority of the thyroid nodules is achieved.


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Female male ratio in thyroid cancer
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Aim
402 patients who were admitted and FNA was done in the Endocrinology Clinic at EBEAH were enrolled in this study. 340 (85%) of them were females and 62 (15%) of them were males. The age range was between 16 and 82. There weren’t any statistical differences in age between both sexes. Thyroid cancer is reported to constitute <2% of cancers in humans. At the same time, it is the most lethal endocrine malignancy. In the literature it is stated that 3% of all cancers in women and 1% of all cancers in men is thyroid cancer. Papillary thyroid carcinoma is the most common malignant neoplasm of thyroid, it generates ~80% of all thyroid cancers.

Results
340 of the examined 402 cases were female and cytopathological results of 303 (89.11%) were benign, 7 (10.88%) were malignant. A total of 62 male patients, 55 (88.70%) were benign, 7 (11.29%) were malignant. Totally 358 cases were reported as benign, 44 cases were reported as malignant. Of the 37 patients who were female, 26 had malignant papillary carcinoma, eight had papillary microcarcinoma, and three had follicular carcinoma. Of the seven male cases which were histopathologically reported as malignant, four had papillary carcinoma, two had papillary microcarcinoma, and one of them was reported as a well-differentiated neoplasm of uncertain malignant potential. When the results of FNAB were analysed according to the gender distribution, there wasn’t any statistically significant difference. The results of FNAB were reported as benign in 89.11% of female and 88.70% of male patients. The positive assessment in terms of malignancy were 10.88% in females and 11.29% in males. Although, in 89.11% of female and 88.70% of male patients.

Conclusions
We described totally five patients whom FNA were malignity but results of postoperative biopsy were benign. We found false positive results as one 38-year-old patient with follicular adenoma, one 50-year-old patient with papillary thyroid cancer, and three patients (44.6± 8.7 years) with suspicious for papillary thyroid cancer. The malignity risk in classification of suspicious for malignity and malignity according to Bethesda reporting system is 60–75 and 97–99% respectively after thyroidectomy. Our findings demonstrate that our false positive results are lower than reported Bethesda classification in medically literature. Hyperplastic adenomatoid nodule, follicular adenoma, well-differentiate follicular carcinoma and papillary carcinoma follicular variant have several characteristic features in common. Therefore, difficulty of these lesions in pathologically evaluation may lead false positive results.

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EP879

Histopathological verification of atypia of undetermined significance in Bethesda system
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The pathologist cannot easily decide some thyroid fine-needle aspiration biopsy (FNA) into the benign, suspicious, or malignity and this condition are reported as ‘atypia of undetermined significance’ (AUS) or ‘follicular lesion of undetermined significance’ in the Bethesda system. Diagnosis of AUS of a thyroid nodule is left an endocrinologist as well as the patients in a difficult situation. However, the risk of malignancy at AUS is ~5–15%. Our aimed to this study is to determined histopathological verification of atypia of undetermined significance according to Bethesda system.

Materials and methods
Results of FNA were used totally in 402 patients with nodular goitre from our hospital records from 2012 to 2014. Twenty people (19 women and one man) out of this study population were diagnosed AUS. All the patients had undergone total or subtotal thyroidectomy. We retrospectively re-evaluated postoperative biopsy results and compared with those histopathological diagnoses.

Results
It was found that postoperative biopsy results of the patients who were diagnosed AUS were adenomatous hyperplasia (5%, n=11), nodular goitre (65%, n=14), papillary carcinoma (5%, n=11), Hashimoto’s thyroiditis (15%, n=3), and microfollicular adenoma (5%, n=1).

Conclusions
Our finding demonstrated that AUS category substantially indicated to benign cellular change. This date was found in accordance with prediction of Bethesda system. Therefore, a repeated FNA should be performed after an appropriate period of time. The factors including follicular lesion in part suspicious follicular neoplasia, existence of lymphoid cell, hypocellularity and artefact of sample preparation may lead to misdiagnosis of malignity in patients with AUS.

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EP880

A pitfall of thyroid fine-needle aspiration biopsy results
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Introduction and aim
Bethesda system for thyroid cytopathology has been widely used recently. Approximately 3–7% of thyroid fine-needle aspiration (FNA) biopsy is considered as malign. Suspicious or malign nodules should likely to be resected. Aim of this study is to confirm the diagnosis of malign or suspicious for malignity according to Bethesda classification in patients with nodular goitre after thyroidectomy.

Materials and methods
Results of FNA in totally 402 patients with nodular goitre were achieved from our hospital records. All of the patients had undergone totally or subtotals thyroidectomy. We re-evaluated retrospectively biopsy results postoperatively. We compared their preoperative FNA results.

Results
We described totally five patients whom FNA were malignity but results of postoperative biopsy were benign. We found false positive results as one 38-year-old patient with follicular adenoma, one 50-year-old patient with papillary thyroid cancer, and three patients (44.6± 8.7 years) with suspicious for papillary thyroid cancer.

Conclusions
The malignity risk in classification of suspicious for malignity and malignity according to Bethesda reporting system is 60–75 and 97–99% respectively after thyroidectomy. Our findings demonstrate that our false positive results are lower than reported Bethesda classification in medically literature. Hyperplastic adenomatoid nodule, follicular adenoma, well-differentiate follicular carcinoma and papillary carcinoma follicular variant have several characteristic features in common. Therefore, difficulty of these lesions in pathologically evaluation may lead false positive results.

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Histopathology results of follicular neoplasia according to Bethesda classification in thyroid fine-needle aspiration biopsy
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Introduction and aim
Interpretation of follicular neoplasia classification according to Bethesda system in thyroid fine needle aspiration biopsy is very different among pathologist. A number of definition including ‘follicular lesion’, ‘follicular proliferation’, ‘follicular lesion of undetermined significance’, and ‘follicular neoplasia’ were used in terminology. A clearly discrimination between nodular goitre, follicular adenoma, and follicular carcinoma cannot lack due to some cytomorphologic features. Approximately 15–50% of case of follicular neoplasia in thyroid fine-needle aspiration biopsy (FNA) is considered as malignity. Aim of this study is to confirm with histopathological diagnosis after thyroidectomy in patients with follicular neoplasia according to Bethesda classification.

Materials and methods
Results of FNA in totally 402 patients with nodular goitre were achieved from our hospital records from 2012 to 2014 years. All the patients had undergone totally or subtotal thyroidectomy. We retrospectively re-evaluated postoperatively biopsy results.

Results
We described ten patients whom diagnosis of FNA were follicular neoplasia but results of postoperative biopsy were adenomatous nodule (n=1),...
Introduction
Medullary thyroid cancer (MTC) could be familial in 30% of cases. Here, we report a family of FMTC with rarely seen RET p.S891A mutation.

Case presentation
A 49-year-old man presented with a single nodule in the left lobe of thyroid. Thyroid ultrasonography (US) showed a nodule and pathological cervical lymph nodes. There was no relevant family history. Fine-needle aspiration cytology (FNAC) of the nodule was consistent with a diagnosis of medullary thyroid carcinoma. Serum calcitonin level was 906 pg/ml (reference range 0–18) and the other laboratory tests, parathyroid hormone level and 24-h urine catecholamine levels were normal. An extensive RET molecular analysis identified the rare intracutaneous RET p.S891A mutation. Then the patient underwent total thyroidectomy and bilateral neck dissection. Histopathology revealed medullary thyroid carcinoma pT1bN1M0 with capsular and lymphovascular invasion and lymph node metastases. Serum calcitonin and carcinoembryonic antigen levels measured 3 months after the surgery was 569 pg/ml and 12 ng/ml respectively. During the follow-up there was progressive rise in calcitonin and CEA levels. No distant metastases were detected. Since there were cervical pathological lymph nodes he was planned to have revision operation. RET p.S891A mutation was also detected at his daughter. She was completely asymptomatic and baseline serum calcitonin and CEA levels were normal. By calcium stimulation test showed no marked increase in CT levels therefore prophylactic thyroidectomy was postponed.

Conclusions
We reported a patient who presented all characteristic features of sporadic MTC but extensive molecular analysis revealed rarely seen intracutaneous RET p.S891A mutation and his daughter had same mutation. RET genetic screening is very important tool for the preclinical diagnosis and early treatment of unsuspected affected family members.

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EP883
Aggressive medullary thyroid cancer in a homogenous population
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Introduction
Medullary thyroid cancer arises from the calcitonin-secreting parafollicular C cells and consists of a spectrum of disease that ranges from extremely indolent tumours, where patients may survive for many years with a large tumor burden, to aggressive types associated with a high mortality rate. The objective of our study is to evaluate the prognostic factors and outcomes of patients diagnosed with medullary thyroid cancer in a homogenous population, and to examine the tissue sample of patients diagnosed with MTC for mutations in the RET proto-oncogene from the same period.

Methods and design
A retrospective analysis of the National Cancer Registry in Ireland was undertaken, for patients with a diagnosis of medullary thyroid cancer between 1998 and 2007. The Kaplan–Meier method was used to determine overall survival and factors predictive of outcome were determined by univariate and multivariate analysis by Cox regression using STATA 13 Software.

Results
Forty-six patients were diagnosed with MTC. 55.8% were females and 44.2% were males. A median age of 52was found. The overall median survival was 6.32 years and the 1- and 5-year overall survival was 88.37 and 62.79% respectively, with a 10-year survival calculated at 48.63%. On univariate analysis age, stage and surgical intervention were statistically significant indicators of prognosis. T stage and age remained statistically significant indicators of prognosis on multivariate analysis. Two patients with no history of MEN syndromes or family history of MTC had RET proto-onocogene mutations.

Conclusions
Our patient cohort was substantially older than what is commonly seen in the literature. There was a very low pick up of RET mutations in sporadic MTC in our patient cohort, and along with relatively poor outcomes, this suggest that further studies of this population may allow us to identify aggressive variants of medullary thyroid cancer.

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EP884
Simultaneous occurrence of medullary and papillary thyroid microcarcinomas: case report
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Thyroid cancers represent ~1% of new cancer diagnoses. Thyroid malignancies are divided into papillary carcinomas (80%), follicular carcinomas (10%), medullary carcinomas (5–10%), anaplastic carcinomas (1–2%), and other rare tumours (primary thyroid lymphomas and primary thyroid sarcomas). The main therapeutic options are surgery (mainly total thyroidecctomy), radiiodine treatment, levothyroxine therapy (TSH suppression dose), others (external beam irradiation, chemotheryapy, and tyrosine kinase receptor inhibitors). A medical investigation was started with a 60-year-old male patient due to palpable thyroid nodules. The ultrasonography revealed nodules in the isthmus and in both thyroid glands (diameter: 4.0, 2.7, and 2.0 cm) without lymphadenopathy, the fine-needle aspiration didn’t show any malignant suspect cytological sign. The patient was euthyroid, the calcitonin level was elevated (38.5 pg/ml, normal: ~9.6). Because of the suspicion of medullary cancer we recommended total thyroidecctomy. The postoperative histology showed papillary microcarcinoma in the left lobe nodule and medullary microcarcinoma in the right lobe nodule with no affected lymph nodes. Levothyroxine therapy was started at substitutional dose, there was no radioiodine treatment. Now the patient has undetectable calcitonin level and low human thyreoglobulin level (<1 ng/ml) with normal anti-human thyreoglobulin rate without any sign of recurrence or metastasis. Genetic screening was performed: it is negative for RET mutation, the other markers are processing. In our case a simultaneous occurrence of medullary and papillary thyroid microcarcinomas were detected in different nodules of the thyroid gland, the genetic screening is in process. In the literature <80 similar cases were reported (none in Hungary). Owing to the rarity of the occurrence we are reporting our interesting case.

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EP885
The utility of basal serum thyroglobulin measurement, using a highly sensitive immunoassay, in the follow up of patients treated for differentiated thyroid cancer
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Introduction
TSH-stimulated serum thyroglobulin (Tg) is used as a sensitive marker for the detection of early recurrence or residual disease following treatment for differentiated thyroid cancer (DTC). However, stimulated Tg, using TSH or thyroid hormone withdrawal, is either costly or cumbersome for patients.

Aim
To compare the performance of basal T4 suppressed, with stimulated Tg measurement, in the follow up of patients treated for DTC.

Methods
We retrospectively reviewed patients treated for DTC at our institution between September 2011 and September 2014. Data recorded included patient demographics, surgical pathology, and imaging results as well as biochemical parameters. Tg was measured by a highly sensitive immunoassay with a functional sensitivity of 0.1 ng/ml. A stimulated Tg >2 ng/ml was considered significant. Patients with an elevated anti-Tg antibody titre were excluded.

Results
46 stimulated Tg measurements were performed in 41 patients – TNM stages 1 and 2 = 33 patients; stages 3 and 4 = 8 patients. Of the 31 tests in which the basal Tg was <0.1 ng/ml, only one (3%) had a stimulated Tg >2 ng/ml; none had radiological evidence of recurrent or residual disease. If the basal Tg was 0.1-0.5 ng/ml, stimulated Tg was >2 ng/ml in 33% of cases.

Conclusion
Undetectable basal Tg measurement, using a highly sensitive Tg assay, together with negative neck imaging, are highly reassuring for remission following treatment for DTC.

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EP886
The introduction of endocrinology–radiology MDT meeting significantly reduced inadequacy rates of thyroid fine-needle aspiration in a University Teaching Hospital
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Aim
A weekly endocrinology–radiology multidisciplinary (MDT) meeting has been recently introduced in our hospital to discuss indications and suitability of thyroid nodules for fine-needle aspiration (FNA). In a recent 5 years retrospective audit, 80% of thyroid FNAs were performed under ultrasound (US) guidance in our institution with an overall inadequacy rate of Thy1 rate of 11.1%.

Objectives
The aim of this study was to assess whether such an intervention can improve percentage of FNAs done under US guidance and reduce inadequacy rates.

Methods
A retrospective review of all computerised meeting records held in 2013. Cytological outcomes for those undergone FNA were obtained from pathology laboratory system.

Results
216 thyroid cases were discussed at our MDT meetings between January and December 2013, of these, FNA was recommended in 118 (54.6%), follow-up US thyroid in 39 (18%), and further images (mainly isotope uptake) in 28 (13%) cases. FNA was not indicated in 31 (14.3%) of cases most of them were small (<1 cm), stable, or hot nodules. 113 thyroid nodules were aspirated following MDT discussion. All FNAs (100%) were performed under US guidance with pathology in attendance to review adequacy of samples. The cytological outcomes were as follows: Thy1 (non-diagnostic) in six (5.3%) cases, Thy2 (benign) in 97 (85.8%) cases, Thy3 (follicular lesion/neoplasm) in seven (6.2%) cases, Thy4 (suspicious for malignancy) in one (0.9%), and Thy5 (malignant) in two (1.8%) cases. Inadequacy rate for FNAs performed following discussion at MDT was significantly lower (5.3%) compared to the overall inadequacy rate of 11.1% reported in the previous audit period (P<0.05).

Conclusion
The introduction of endocrinology–radiology MDT meeting resulted in a 52.3% reduction of thyroid FNA inadequacy rate. This MDT proved to be a cost effective intervention in reducing inadequacy rate, hence further costs. All thyroid nodules should be discussed at such meeting to assess suitability for FNA.

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EP887
Value of neutrophil to lymphocyte ratio in predicting malignancy in thyroid nodules diagnosed as follicular neoplasm on cytology
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Aim
It is well known that there is a strong relationship between chronic inflammation and tumorigenic process. The cytological diagnosis of follicular neoplasm (FN) carries a 20–30% risk of malignancy for thyroid nodules. In this study, we aimed to evaluate whether preoperative neutrophil to lymphocyte ratio (NLR) is a predictive factor for malignancy in thyroid nodules diagnosed as FN on cytology.

Materials and methods
A total of 139 patients with FN who were treated by surgery were enrolled. Preoperative demographic and laboratory findings, USG characteristics and final pathological results were assessed retrospectively.

Results
86.3% of the patients are females (n=120) and 13.7% are males (n=19). The overall malignancy rate of FN cytology was 44.5% (n=62). There was no significant difference in NLR between the benign and malign groups (NLR=2.12±1.05 and 1.98±0.92, respectively, P=0.496). When USG features were evaluated, hypoechochogenicity and irregular margins was found associated with malignancy risk (P=0.006).

Conclusion
Our study showed no association between NLR and malignancy risk in thyroid nodules diagnosed as FN on cytology. The NLR is used as a readily available and inexpensive biomarker of inflammation. Many studies emphasised the increased NLR is associated with poor prognosis and adverse survival in various solid tumors including differentiated thyroid tumors. But we concluded NLR is not useful in predicting malignancy risk of thyroid nodules diagnosed as FN on cytology.

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Papillary thyroid carcinoma: 33 years of experience of a single institution in Serbia
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Introduction
Well-differentiated thyroid carcinoma in children is rare but it shows aggressive behaviour. Gross lymph node metastases and distant metastases are common on first clinical presentation. Patients and methods
During 33 years (1981–2014) at the Institute of Oncology and Radiology of Serbia 24 children were operated due to papillary thyroid carcinoma. Mean age was 12.6 (range 7–16) years. At the time of diagnosis 12.5% patients had lung metastases. Total thyroidectomy or completion of thyroidectomy was performed in all cases followed with central neck dissection and frozen section examination of the jugulo-carotid compartments. Median follow-up was 10.1 (range 2.0–29.4) years.

Results
pT1a tumors were found in 12.5%, pT1b in 25%, pT2 in 20.83%, and pT4 in 16.67%. All patients had papillary thyroid carcinoma. Multifocal tumours were found in 79.17% and capsular invasion in 83.33%. Lymphonodal metastases and distant metastases are common on first clinical presentation. Patients and methods
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Results
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Conclusion
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Well-differentiated thyroid carcinoma in children is rare but it shows aggressive behaviour. Gross lymph node metastases and distant metastases are common on first clinical presentation.
Introduction
Papillary thyroid carcinoma (PTC) is the most frequently occurring subtype of thyroid differentiated cancers. PTC frequently metastasizes to the cervical lymph node region and metastasis rate of approximately 20-90% is available when diagnosed. Distant metastases are usually the lungs, bone and brain metastases. Furthermore rarely are the adrenal gland, skeletal muscle, ovariary, submamillar gland, sphenoid sinuses, liver and pancreatic metastases can be occurred. PTC’s lung metastases can manifest as nodular, local or generalized lymphadenopathy, pleural effusion and miliary multiple metastases. Miliary metastases are extremely rare. Case A 40-year-old man was referred to Department of Pulmonary Diseases for complaints of cough with expectoration, dispnea and chest pain. Chest x-ray revealed milary pulmonary lesions which was confirmed on computed tomography (CT) analysis. Because of clinical suspicion of miliary tuberculosis, bronchosopic biopsy was performed. The papillary thyroid cancer metastasis was diagnosed in histological examination. Since the histological diagnosis was PTC, we checked the thyroid gland. Ultrasound examination of thyroid gland showed 10×15 mm hypoechoic solid nodule with micro calcification. The diagnosis of PTC was verified with cytological examination via ultrasound guided thyroid fine needle aspiration. Because of these findings total thyroidectomy was performed. Microscopically, this node was diagnosed PTC (bristle cell variant) with capsular and lenfovascular invasion. After treatment with iodine 131 was planned patient was discharged. Conclusion Although PTC is known relatively lingering disease, the early metastases can be occurred before When diagnosis of PTC is established. Metastatic PTC may appear radiographically as solitary or multiple nodules and rarely diffuse micronodular and reticular. So because of these patterns while evaluating the miliary lesions of lung the metastases of PTC must be come to mind.

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Lymphocytic thyroiditis and differentiated thyroid cancer – challenges in follow-up
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Introduction
Chronic lymphocytic thyroiditis (LT) is a very common condition, and its coexistence with papillary thyroid carcinoma has often been reported. Analytical and echographic challenges must be kept in mind in the follow-up of patients with both these disorders.

Case report:
We present the case of a woman with a history of multinodular goitre who underwent left thyroidectomy and isthmectomy at the age of 43, with the histopathological finding of papillary microcarcinoma associated with nodular hyperplasia and LT. Her follow-up included regular cervical and thyroid ultrasound and thyroglobulin (Tg) and antithyroglobulin autoantibodies (TgAbs) measurements. The remaining right thyroid lobe had a micronodular appearance on ultrasound; TSH was in the normal range; TgAbs were positive; Tg was undetectable. After 8 years of follow-up, ultrasound revealed a suspicious cervical lymph node. A fine-needle aspiration biopsy (FNAB) was performed, with the Tg concentration of FNAB washout liquid being 36 ng/ml and cytology revealing aspects of metastasis from papillary thyroid carcinoma. She underwent completion thyroidectomy and lymph node dissection. Histopathology revealed a 12 mm papillary carcinoma in the right thyroid lobe, with extension to perithyroidal adipose tissue. The patient was subsequently admitted for radioiodine remnant ablation.

Conclusions
In patients with thyroid papillary microcarcinoma who have had only partial thyroidectomy and are positive for TgAbs, neither Tg nor TgAbs can be used reliably; careful ultrasound examination is essential in the follow-up of these patients. On the other hand, due to known alterations in thyroid gland structure, LT may cause diagnostic performance of thyroid ultrasound to be inferior in detecting suspicious nodules. This case report brings attention to the different difficulties found in the follow-up of patients with coexisting LT and thyroid papillary carcinoma.

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Cytological variants of papillary thyroid carcinoma: clinical presentations according with the presence of BRAF mutation
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Introduction
BRAF(V600E) mutation has received great attention to improve risk stratification in patients with PTC. Its prognostic value in the different Cytological variants (CVs) of PTC is not well established. The aim of this study was to investigate differences in clinicopathological features according to CV type, among patients harbouring the mutation.

Methods
We evaluated 102 patients with pathological diagnosis of PTC. All of them underwent total thyroidectomy and radioiodine ablation, 87 central lymph node (LN) dissection (67 prophylactic, and 18 lateral neck dissection as well. DNA was extracted from neoplastic cells and BRAF mutation was detected by PCR and sequencing. Analysis included histological subtype, age, multifocality (MF), extrathyroidal extension (EET), LN metastases (LNMx), LN ratio (LNR) number (of positive LN divided by the total amount of dissected nodes) and clinical remission (CR) after 1 year of initial treatment (stimulated thyroglobulin (Tg) undetectable, no presence of Tg antibodies and negative cervical ultrason).

Results
Patients harboured BRAF mutation (45,1%). According to CV type, CV2/3 (71%) and classic variant (CV), 3/3 (9%) follicular variant (FV) and 16/25 (64%) mixed forms (MF). In mutation carriers mean age was 47 years in CV, 58 in FV and 60 in MF. PV was present in 59% of CV, 66% FV, 50% MF. EET was found in 51% of CV, 33% FV, 33% MF. The rate of central LNMx was 85% in CV, 37%MF and no patients in FV. The LNR was 22.4% in CV, and 6.1% in MF. CR was achieved in 15 out of 20 evaluated patients with CV and all the 11 with MF.

Conclusions
In our series BRAF mutation is more prevalent in CV of PTC as it has been described previously, and at a younger age. We also emphasise the high prevalence of LNMx and the higher LNR found in patients with CV tumours. Given the prognostic value of BRAF mutation, these results confirm the more benign behaviour of FVPTC.

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Incidence and peculiarities of thyroid cancer in patients with type 2 diabetes mellitus
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Diabetes mellitus is a risk factor for cancer, specifically of breast, endometrium, bladder, liver, colorectum, and pancreas. The pathophysiology of how diabetes contributes to cancer growth or development is an area of active investigation. The aims is to study the frequency and morphological features of thyroid cancer in patients with type 2 diabetes mellitus (DM).

Results
Data was gathered from the patients’ medical records in the Department of Endocrinology and Metabolism at the Transplantation of Endocrine Organs and Tissues. The study involved 980 patients with thyroid cancer and type 2 DM. Among patients with thyroid cancer and type 2 DM, 980 patients were included after excluding patients who did not undergo treatment at the surgical department of the Ukrainian Scientific and Practical Center of Endocrine Surgery for the period from 2010 to 2012 years. The examination included the study of patients’ complaints, measurement of blood glucose profiles, glycated hemoglobin, immunoreactive insulin (IRI), C-peptide, HOMA-IR index, lipid profile, thyroid ultrasound and abdominal organs. In addition conducted fine needle aspiration of thyroid nodules before surgery, pathological examination after surgical treatment, the determination of interleukin-6 (IL-6). We studied the incidence of thyroid cancer in the general population of Ukraine. Statistical data were processed using Microsoft Excel. Results are expressed as the mean ± standard error indicators (M ± m).

Results
The mean age of patients with type 2 DM and thyroid cancer was 59.2 ± 2.7 years, duration of DM (from the time of diagnosis) – 7.1 ± 1.3 years, body mass index (BMI) – 17.1 ± 2.6 kg/m². All patients established insulin resistance (IRI level was 31.26 ± 2.81 µU, HOMA-IR index – 14.57 ± 2.31). The frequency of type 2 DM among all patients treated with thyroid cancer and DM is 4.6%. Among patients with thyroid cancer and type 2 DM were mostly women (32; 71.1%). Most patients had papillary thyroid cancer (37; 82.2%) than follicular one. Among the total
population of Ukraine thyroid cancer had been diagnosed in 39,042 patients, representing 74.8 per 100,000. At the same time among the inhabitants of Kiev incidence of thyroid cancer reaches 3039 (177.5 per 100,000). Obviously that the presence of DM is associated with an increased risk development of thyroid cancer. The number of newly diagnosed patients with thyroid cancer in Ukraine increase and in 2011 was 2984, or 6.5 per 100,000 of population, but in some regions, for example, in Kiev and the Kiev region, the incidence is respectively 12.9 and 12.2 per 100,000 of population.

Conclusion
Patients with DM have a higher incidence of thyroid cancer compared with the general population. The frequency of type 2 DM among patients with thyroid cancer is 4.6% with a predominance of women (71.1%). Most patients had the papillary thyroid cancer (82.2%) than follicular one.

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EP900
Concomitant thyroid nodules in primary hyperparathyroidism
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Objectives
Coexisting thyroid nodules affect the treatment choice for PHPT. We aimed to evaluate the incidence of concomitant thyroid nodules in patients with primary hyperparathyroidism and to investigate the relationship between thyroid nodule volume, thyroid gland volume and thyroid nodules with clinical and laboratory parameters.

Materials and methods
This study was carried out at Ankara University Endocrinology and Metabolism Department. 183 patients with biochemically confirmed primary hyperparathyroidism and 30 patients with no any other co-morbidities, as a control group, were evaluated. USG images, FNAB results, clinic and laboratory parameters of patients were reviewed from medical data.

Results
Thyroid nodules were higher in the PHPT patients (P < 0.001). Six of the patients had papillary thyroid carcinoma and one had follicular neoplasia. Patients with thyroid nodules had higher 25-OH vitamin D levels (P = 0.026). Thyroid volume was positively correlated with BMI (P = 0.001, r = 0.272), fasting glucose (P = 0.02, r = 0.173) and negatively correlated with TSH (P = 0.01, r = -0.194). Number of nodules and nodule volume were positively correlated with creatinine (P = 0.036, r = 0.158) and negatively with GFR (P = 0.018, r = -0.179). Also nodule volume was positively correlated with 25-OH vitamin D level (P = 0.04, r = 0.154). In regression analyses thyroid volume was found to be in relation with creatinine, HDL, 24 h urinary calcium and phosphorus; number of nodules with age, creatinine, GFR, BMI, HDL, 25-OH vitamin D, albumin and 24 h urinary calcium. The patients with malignancy had higher T4 lower TSH and better P
time. The patients with malignancy had higher T4 lower TSH and better

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EP902
Evodiamine inhibits human thyroid cancer cells in vitro and in vivo
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Thyroid cancer is the most prevalent cancer among endocrine malignancies. In clinically, surgical resection combined with radioactive iodine therapy has been proven effective in treating differentiated thyroid cancer, including papillary and follicular thyroid cancers (FTC). However, patients with incurable differentiated thyroid cancer (DTC), poorly differentiated thyroid cancer (PDTC) and anaplastic thyroid cancer (ATC) exhibit worse prognosis. Therefore, a novel and effective treatment is urgently needed to deal with the current treatment. Evodiamine is one of the important components isolated from Chinese herb Wu-Chu-Yu, and has been demonstrated to contribute on anti-inflammatory effects, anti-angiogenesis, anti-tumor growth, anti-invasive and metastatic activities, and up-regulating apoptosis. In the present study, we examined the effects of evodiamine in FTC, PDTC and ATC cells, respectively. Evodiamine inhibited cellular proliferation and the colonies formation of FTC, PDTC and ATC cells. Cell cycle arrest at G2/M phase was found in all of the cells during evodiamine treatment. Moreover, caspase-dependent apoptosis in these cells was also revealed under evodiamine treatment. In addition, autophagy induction was also found in evodiamine treated human thyroid cancer cells. Finally, we verified the effects of evodiamine on anti-human thyroid cancers in a xenograft nude mice model. Our results demonstrate that evodiamine induces cell cycle arrest, caspase-dependent apoptosis and autophagy leading to inhibit proliferation of multiple types of human thyroid cancer cells. We suggest that evodiamine could be a chemo-therapeutic candidate for human thyroid cancers.

Disclosure
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Familial non-medullary thyroid cancers tend to be more bilateral and have more capsular invasion compared to non-familial ones

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Introduction
Currently, about 5–15% of non-medullary thyroid cancers (FNMC) are considered to be of familial origin. These are either syndrome-associated tumours or non-syndromic tumours. The aim of the study was to determine the clinical, pathological and biochemical characteristics of FNMC compared to non-familial ones with a follow-up of 10 years.

Methods
Among FNMC T followed by a single physician, 62 patients with papillary cancer were screened retrospectively.

Results
(40.3%) patients had either one or more of their first-degree relatives with papillary cancer. Age (48.1 ± 15.1 years vs 45.3 ± 13.1 years), female/male ratios (20/5 vs 28/9) and age at diagnosis (44.1 ± 12.1 yrs vs 39.4 ± 10.9 years) were similar. Bilateral tumours (7/25 vs 5/37, P = 0.01) and capsular invasion (11/25 vs 9/28, P = 0.004) were more frequent in FNMC compared to non-familial ones. Maximum tumour diameter (0.9 ± 2.6 cm vs 1.3 ± 1.0 cm) was comparable. Multicentricity (8/25 vs 8/37), lymph node metastasis (5/25 vs 6/37), vascular invasion (5/25 vs 5/37 patients), number of patients being operated more than once (4/25 vs 8/37 patients), having radioiodine therapy (10/25 vs 13/37), having classical tumour subtypes (11/25 vs 15/37) were comparable among groups. Postoperative thyroglobulin (0.48 ± 1.02 vs 0.65 ± 1.48) and TSH levels (0.16 ± 0.26 vs 0.25 ± 0.45) at 1st and (0.31 ± 0.44 vs 0.44 ± 0.76 thyroglobulin and 0.02 ± 0.03 vs 0.32 ± 0.69 TSH) 5th year follow-up were comparable. When patients with two cases (n = 20) and more than two cases in family (n = 8) were compared, all above mentioned parameters were similar among groups.

Conclusion
In conclusion, FNMC tends to be more bilateral and has a higher rate of capsular invasion compared to non-familial ones.

DOI: 10.1530/endoabs.37.EP903

Adjuvant radioiodine (RAI) treatment reduces the risk of relapse in low advanced differentiated thyroid carcinoma (DTC)

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The routine use of adjuvant RAI treatment in non-medullary thyroid cancers reveals controversy due to the lack of unequivocal evidences of its effectiveness in radically operated patients. The aim of the study was to retrospectively evaluate the outcome of adjuvant RAI treatment in low-risk (T1–T3, N0Nx and Tg < 10 ng/ml), 90 as high risk (stimulated Tg > 30 ng/ml), whereas 148 remaining patients (92%) a successful ablation at 6-month efficacy control was achieved. One patient (5.1 ng/ml stimulated Tg) was re-treated with a new dose of 30 mCi and a second patient (2.3 ng/ml stimulated Tg) spontaneously normalised her basal and stimulated Tg levels at the 18-month control. Dosimetry on family members showed exposure levels of < 0.2 mSv.

Conclusion
The post-surgical outpatient treatment with an activity of 1100 MBq is safe for the family environment and cost-effective in a great majority of patients with low-risk FTC. Ablation was considered successful when no abnormal activity was observed in WBS and SPECT-CTs and when basal/stimulated thyroglobulin levels were under 1 and 2 ng/ml, respectively.

Results
All 25 patients showed thyroid uptake without uptaking adenopathies in the WBS and SPECT-CTs performed on the fifth day. Control of therapeutic efficacy was performed at 6 months, using WBS and SPECT-CT with 111In. Two patients (2/25) were not retreated with a new dose of 30 mCi and a second patient (2.3 ng/ml stimulated Tg) subsequently normalised her basal and stimulated Tg levels at the 18-month control. Dosimetry on family members showed exposure levels of < 0.2 mSv.

Conclusion
The postsurgical outpatient treatment with an activity of 1100 MBq is safe for the family environment and cost-effective in a great majority of patients with low-risk FTC. The postsurgical outpatient treatment with an activity of 1100 MBq is safe for the family environment and cost-effective in a great majority of patients with low-risk FTC.

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EP905
Efficacy and safety of an outpatient low radioiodine dose for remnant thyroid ablation in low risk papillary thyroid carcinoma (PTC)

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In PTC, radioiodine required dose for thyroid remnant ablation is uncertain. Recent works show that low doses may be sufficient for low risk patients.

Aim
To evaluate the efficacy and safety of thyroid remnant ablation in patients with low-risk PTC by using 1100 MBq (30 mCi) outpatient doses.

Materials and methods
Twenty-five patients (24 women, 55 years-old mean age, range 34–77) referred to our department to be treated with low-risk PTC were evaluated. Radioiodine ablation was performed in the outpatient clinic under rhTSH stimulation with strict radiation protection measurements and dosimetry control at home environment. Whole body scan (WBS) and SPECT-CT were performed on the fifth day.

Results
A total of 10 patients (40%) were found to be positive at 6 months follow-up. The mean dose of radioiodine used was 1100 MBq.

Conclusion
The use of low radioiodine dose for thyroid remnant ablation in low-risk PTC is feasible and safe.
**EP907**

**Wide screening of RET proto-oncogene in Iranian medullary thyroid carcinoma patients: 13 years study**

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**Introduction**

Thyroid cancer is the most common endocrine cancer and medullary thyroid carcinoma (MTC) is one of the most malignant thyroid tumours which occur in both hereditary (25%) and sporadic (75%) forms. Mutations of the RET proto-oncogene in MTC development have been well demonstrated. The aim of the study was to investigate the mutational spectrum of exons 3, 5, 8, and 10–18 of the RET proto-oncogene in MTC patients.

**Material and methods**

This retrospective study has been started since 2001 in Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran. 399 participants, including 233 patients (176 sMTC, 40 FMTC, eight MEN2A, four MEN2B, five pheochromocytoma), and 166 relatives were evaluated. Genomic DNA was extracted by the standard Salting Out/Proteinase K method and Mutation detection was performed through direct DNA sequencing. Sequence analysis was performed by Chromas Software version 2.3.

**Results**

Totally, in 233 patients (131 female, 102 male) and 166 relatives (91 female, 75 male), 82 mutations were identified in RET main exons, including 10, 11, and 13–16. Furthermore, 282 single nucleotide polymorphism (SNP) were found in exons 3, 13, and 14. Interestingly, G691S SNP and S904S SNP were 100% in linkage disequilibrium in 131 patients and 87 relatives. The most common mutation in our population were C634Y and C634R (4%) whereas C618R, C618S, C620G, L857R mutations had rare allele frequency (0.3%). Moreover, R886Q mutation was detected in exon 15 in two members of a family affected with MTC for the first time.

**Discussion**

Exon 11 and after that exon 10 were the most frequently mutated exons of RET proto-oncogene in MTC patients in Iranian population. As about half of patients with the hot spot mutations had the G691S/S904S haplotype simultaneously, further analysis needs for clarifying the effect of multiple risk alleles in MTC development.

**DOE**: 10.1530/endoabs.37.EP907

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**EP908**

**Ratio of lymph node aspiration washout thyroglobulin levels to whole blood and serum washout thyroglobulin levels in patients with differentiated thyroid carcinoma: a new approach for standardisation of measurements and increased accuracy**

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**Introduction**

High values of fine needle aspiration washout thyroglobulin (FNA-Tg) are diagnostic for metastatic lesions of thyroid cancer. However, there is not a consensus on cut-off for high Tg level. The most important confounding factor for FNA-Tg is inability to calculate Tg per unit volume because residual aspiration material in the needle cannot be known exactly. Another problem is possible contamination of whole blood during lymph node aspiration. In this study, we aimed to determine a more accurate and standardised parameter for FNA-Tg.

**Methods**

Ultrasonographically suspicious 155 lymph nodes in 120 patients with histopathologically confirmed differentiated thyroid cancer and suspicious for malignancy/malignant thyroid nodule were evaluated. Tg was measured in samples obtained by aspiration (FNA) and non-aspiration (FNNA) biopsy. The highest value obtained by these methods from the same lymph node was defined as FNB-Tg. Simultaneous venous blood sample was taken. Tg was measured from whole blood and serum washouts which were obtained by using syringes and needles identical to ones used for lymph node biopsy.

**Results**

Data of 16 lesions in 14 patients who underwent lymph node dissection were analysed. FNNA-Tg, FNB-Tg/whole blood washout-Tg, FNB-Tg/serum washout-Tg, FNB-Tg/whole blood washout-Tg, FNNA-Tg/serum washout-Tg, were statistically significant for the discrimination of benign and malignant lymph nodes. Best cut-off values for FNNA-Tg and FNB-Tg were 15.86 and 31.8 ng/ml, respectively. Among ratios, best cut-off values to discriminate benign and malignant lymph nodes were 5.44 for FNB-Tg/whole blood washout-Tg and 3.95 for FNB-Tg/serum washout-Tg.

**Conclusion**

Determineing ratio of FNB-Tg to whole blood washout-Tg and/or serum washout-Tg might be a promising method for increasing accuracy and providing standardization of lymph node aspiration to detect malignant lymph nodes.

**DOE**: 10.1530/endoabs.37.EP908

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**EP909**

**The role of thyroid cancer (TC) in a thyroid nodule on the basis of a tertiary reference TC center experience**

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**Background**

A global TC risk in a single thyroid nodule is rather small and ranges between 1 and 11%. However, taking into consideration Bethesda System for Reporting Thyroid Cytopathology TC risk varies between distinct categories: 0–3, 3–5, 5–15, 15–30, 30–60 and 60–99% for Bethesda class II–VI, respectively. However, these values may differ in a centre, specialized in TC. Therefore, the aim of this study was to evaluate the TC risk in patients referred to a tertiary reference TC centre.

**Material and methods**

This retrospective study has been started since 2001 in Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, and Tehran, Iran. 399 participants, including 233 patients (176 sMTC, 40 FMTC, eight MEN2A, four MEN2B, five pheochromocytoma), and 166 relatives were evaluated. Genomic DNA was extracted by the standard Salting Out/Proteinase K method and Mutation detection was performed through direct DNA sequencing. Sequence analysis was performed by Chromas Software version 2.3.

**Results**

Totally, in 233 patients (131 female, 102 male) and 166 relatives (91 female, 75 male), 82 mutations were identified in RET main exons, including 10, 11, and 13–16. Furthermore, 282 single nucleotide polymorphism (SNP) were found in exons 3, 13, and 14. Interestingly, G691S SNP and S904S SNP were 100% in linkage disequilibrium in 131 patients and 87 relatives. The most common mutation in our population were C634Y and C634R (4%) whereas C618R, C618S, C620G, L857R mutations had rare allele frequency (0.3%). Moreover, R886Q mutation was detected in exon 15 in two members of a family affected with MTC for the first time.

**Discussion**

Exon 11 and after that exon 10 were the most frequently mutated exons of RET proto-oncogene in MTC patients in Iranian population. As about half of patients with the hot spot mutations had the G691S/S904S haplotype simultaneously, further analysis needs for clarifying the effect of multiple risk alleles in MTC development.

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**Endocrine Abstracts (2015) Vol 37**
Material
282 thyroid nodules were involved into a retrospective analysis. Fine needle aspiration biopsy (FNAB) was performed in all cases and followed by surgery regardless of the results of FNAB. Next, histopathological findings were compared with FNAB results.

Results
According to FNAB 26.9% thyroid nodules were classified as benign (Bethesda II), 28.7% as malignant (Bethesda III), while 23.8% as indeterminate (Bethesda III+IV-V). Among indeterminate nodules 3/67 were diagnosed as Bethesda III, 23/67 as follicular neoplasm (Bethesda IV), whereas 41/67 were suspicious for malignancy (Bethesda V). For 20.6% remaining tumours the FNAB result was non-diagnostic (Bethesda I). TC was diagnosed by histopathological examination in 171 tumours (60.6%), among them in 21/76, 39/67, 81/81 and 36/58 preoperatively classified as benign indeterminate, malignant and non-diagnostic, respectively. 96 nodules were benign in histopathology, while for 15 others no data were available. Finally, the risk of TC evaluated on the basis of aforementioned data was 27.6% for benign nodules, 39.1% for follicular neoplasm, 70.7% for nodules suspicious for malignancy and 100% when tumour were classified as malignant. Surprisingly, TC was confirmed after surgery in 51.7% with non-diagnostic FNAB.

Conclusions
The risk of TC in thyroid nodules referred to specialised thyroid cancer center is substantially higher than in routine practice. Thus, more careful procedures, including molecular markers are necessary to state a proper diagnosis and start the treatment on time.

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EP910

Thyroid cancer in Ireland: a 10-year review of the National Cancer Registry
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Introduction
The increased incidence of thyroid cancer is driven mainly by a large increase in papillary thyroid cancer (PTC). The number of patients that succumb to the disease has remained stable. The aim of our study is to analyze the incidence and mortality of thyroid cancer in Ireland.

Methods and design
A retrospective analysis of the National Cancer Registry was undertaken, between 1st of January 1998 and the 31st December 2007. The Kaplan–Meier method was used to determine overall survival using Stata 13 software.

Results
A total of 949 patients were diagnosed, 781 (82.2%) were well-differentiated thyroid cancer (papillary 565, follicular 177, Hurtle cell 39) whilst there were 44 medullary thyroid cancers and 61 anaplastic thyroid cancers. The female to male ratio was 3:1, with a median overall age of 47. This was significantly lower in medullary thyroid cancers and anaplastic thyroid cancers. There were also a significantly more nodules with a non-diagnostic result in the Group A ($\chi^2$ test, P<0.001). There were also a significantly more nodules with a non-diagnostic result in the Group B ($\chi^2$ test, P<0.01) than in Group B (33% vs 25% respectively). The Benign lesions and follicular Neoplasm were significantly more frequent in Group B (59.1 and 1.5%) when compared to Group A (55.0 and 0.6%), ($\chi^2$ test, P<0.001 for benign lesions; P<0.05 for follicular neoplasms). There was no significantly difference in the results of atypia of undetermined significance, suspicious for malignancy and malignant with or without CT.

Conclusions
The presence of a CT had an impact on results of FNAC, diminishing the number of non-diagnostic results and increasing the results of benign lesions and follicular neoplasms.

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EP912

Proprotein convertase subtilisin/kexin type 9 (PCSK9), soluble lectin-like oxidized LDL receptor 1 (SLOX-1) and ankle brachial index in short term overt hypothyroidism
Cigdem Ozkan1, Muşle Aktürk1, Alev Ergolu Altinova1, Ethem Turgay Cerel1, Ozlem Gulbahar1, Mehmet Muhittin Yalcin1, Nuri Cakir1 & Fusun Balos Toruner1
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Cardiovascular deleterious effects of short term hypothyroidism are not well known. We aimed to investigate proprotein convertase subtilisin/kexin type 9 (PCSK9), soluble lectin-like oxidized LDL receptor 1 (SLOX-1) and ankle brachial index (ABI) in patients with thyroid cancer with short term overt hypothyroidism due to thyroid hormone withdrawal (THW). Twenty-one patients who require radioactive iodine (RAI) ablation or RAI scan and thirty-six age, sex, BMI similar euthyroid healthy control subjects were enrolled into this study. Patients were evaluated both in subclinical thyrotoxic period when they were on suppressive levothyroxine therapy and overt hypothyroidism period due to THW for four weeks. Serum PCSK9, SLOX-1, lipid levels and ABI were measured in patient and control groups. Total cholesterol, LDL cholesterol, triglycerides and Apo B levels were increased in short term overt hypothyroidism compared to control group (P<0.001). Patients with short term overt hypothyroidism had significantly increased PCSK9 levels compared to control group (P<0.001). PCSK9 levels were also found to be increased before THW when compared to control group (P=0.004). SLOX-1 levels were not different between patients with short term overt hypothyroidism and control group (P=0.27). ABI was found to be significantly decreased in patients with short term overt hypothyroidism compared to control group (P=0.02). In conclusion, we found increased PCSK9 and decreased ABI which may contribute to the undesirable metabolic and vascular changes in thyroid cancer patients with short term overt hypothyroidism due to THW.

DOI: 10.1530/endoabs.37.EP912
EP913 Thyroid malignancy risk of incidental thyroid nodules in patients with non-thyroid cancer
Mehmet Yalcın1, Alev Altinova1, Cigdem Ozkan1, Fusun Balos Toruner1, Mojde Akturk1, Ozgur Akdemir1, Yucel Emiroglu1, Derda Gokce1, Ayta Poyraz2, Ferit Taneri3 & Ilhan Yerkin1
1Department of Endocrinology and Metabolism, Faculty of Medicine, Gazi University, Ankara, Turkey; 2Department of Nuclear Medicine, Faculty of Medicine, Gazi University, Ankara, Turkey; 3Department of Internal Medicine, Faculty of Medicine, Gazi University, Ankara, Turkey; 4Department of Pathology, Faculty of Medicine, Gazi University, Ankara, Turkey; 5Department of General Surgery, Faculty of Medicine, Gazi University, Ankara, Turkey.

Objective
Thyroid incidentaloma is a common endocrinological disorder. Current literature regarding the risk of thyroid cancer in incidentalomas found in patients with non-thyroid cancer is limited. The aim of the present study was to investigate the frequency of thyroid malignancy in incidentalomas detected in patients with non-thyroid cancer.

Methods
The database of 287 thyroid nodules from 161 patients with a history of non-thyroid cancer followed between 2008 and 2014 were retrospectively evaluated. From 287 thyroid nodules, 69.7% had a benign final cytology. Thyroid cancer detected in one nodule while follicular neoplasia detected in four nodules, atypia of unknown significance (AUS) detected in ten nodules, hurthle cell neoplasia detected in five nodules and suspicious for malignancy detected in six nodules according to fine needle aspiration biopsy results. Metastasis of the non-thyroid cancer to the thyroid gland were detected in four nodules. Twenty seven nodules from 15 patients were removed with surgery. There were three malignant nodules found after surgery (one papillary, one follicular and one medullary cancer). In addition to these three thyroid cancers, two patients with benign nodules had co-incident thyroid cancer detected after surgery. Finally, 11.1% of thyroid nodules which underwent thyroid surgery had malignant histopathology except co-incident and metastatic cancers.

Conclusion
The frequency of thyroid malignancy seems not to be substantially increased in incidental thyroid nodules detected in patients with non-thyroid cancer when these patients were evaluated in nodule-based approach.

DOI: 10.1530/endoabs.37.EP913

EP914 Differentiated thyroid cancer: assessment of clinical practice in a tertiary referral centre
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International best practice guidelines provide well-defined recommendations for the management of differentiated thyroid cancer (DTC) measuring ≤ 1 cm, > 4 cm and for those with defined risk factors. However, the extent of surgery and requirement for radioactive iodine remnant ablation (RRA) are less clearly defined for tumours 1–4 cm in size. Guidelines recommend a ‘personalised decision making’ approach for this cohort, with therapeutic decisions based on patient preference, recurrence risk and multi-disciplinary discussion. This study aims to assess adherence to guidelines and investigate treatment patterns in the ‘personalised decision making’ cohort for thyroid cancers in an Irish tertiary referral centre. A random subset of 97 patients treated for DTC between 2009 and 2014 were assessed. Data were obtained from a prospectively maintained thyroid cancer database. 92 out of 97 patients (95%) were managed in accordance with guidelines (Table 1). Out of those whose management did not adhere to guidelines, three were overtreated with total thyroidectomy, while two were under treated with lobectomy only. 28 patients (29%) had tumour characteristics requiring ‘personalised decision making’, 26 underwent total thyroidectomy rather than lobectomy. Similarly for RRA, 39 out of 41 patients (95%) in the ‘personalised decision making’ group were treated with radioactive iodine.

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Table 1.

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Adherence to guidelines (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cohort:</td>
<td>97 (100)</td>
</tr>
<tr>
<td>≤ 1 cm</td>
<td>17 (18)</td>
</tr>
<tr>
<td>1–4 cm</td>
<td>61 (63)</td>
</tr>
<tr>
<td>&gt; 4 cm</td>
<td>19 (20)</td>
</tr>
<tr>
<td>Multifocal</td>
<td>40 (41)</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td>21 (22)</td>
</tr>
<tr>
<td>Capsular invasion</td>
<td>21 (22)</td>
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</tbody>
</table>

These data suggest that management of thyroid cancer at our institution closely adheres to guidelines, with a trend towards more aggressive management in those where personalised decision making is required.

DOI: 10.1530/endoabs.37.EP914

EP915 Graves’ disease and papillary/insular thyroid cancer in a large compressive goitre
Mara Carsoe1, Anda Dumitrascu2, Dana Terzec1, Andreea Geleriu2, Dan Petretian1, Daniela Alexandrescu2, Corina Chirita2, Radu Iorgulescu3, Andrei Goldstein2 & Catalina Poiata1,2
1C. Davila University of Medicine and Pharmacy, Bucharest, Romania; 2C.I. Parhon National Institute of Endocrinology, Bucharest, Romania; 3CM Povarnei Medical Centre, Bucharest, Romania; 4St John Hospital, Bucharest, Romania; 5Monza Oncoteam Hospital, Bucharest, Romania; 6Anima Medical Centre, Bucharest, Romania.

Introduction
The association between autoimmune thyroid disease and thyroid cancer is a dynamic field regarding the prevalence data and the common pathogenic background. We report a sixth decade women case with a 1 year history of Graves’ disease that was discovered with an aggressive differentiated thyroid carcinoma.

Case report
M.E. 56-year-old female has a 10 months history of daily medium dose of thiamazolum which was well tolerated (she presented with mild features of hyperthyroidism). The personal and family medical history is negative. On admission, she accused compressive symptoms for the last 2 months. The TSH was 1.59 μU/ml. The eye examination showed values of 17 mm for proptosis. The cervical computed tomography pointed a large left thyroid nodule of 4.5 by 7.28 cm, with multiple microcalcifications associating a mass effect over the trachea (the minimum diameter of 1.71 by 1.7 cm at the level of clavicles). The eye exam showed values of 17 mm for exophthalmometria. The calcitonin was normal (of 0.857 pg/ml) , as well as antithyroperoxidase antibodies (of 14 U/ml). The total thyroidectomy and lymph neck resection was performed. A papillary thyroid carcinoma (oxifile type) with insular and compact areas was found (of 6 cm), together with vessel invasion (T3N1Mo). The immunohistochemistry pointed a Ki67 of 15%. The 131 iodine therapy was added to the levothyroxine suppressive therapy.

Conclusion
The finding of a follicular cells cancer in a thyroid underlining an autoimmune process is a rare event, yet new data reveals that the two diseases maybe more than incidental, possibly by sharing common mechanisms.

DOI: 10.1530/endoabs.37.EP915

EP916 Differentiated thyroid carcinoma prevalence in the Graves’ disease; Akdeniz University experience
Mustafa Kemal Balci, Bisren Unsal Koyuncu, Safiye Arik, Cumhur Arıcı, Ramazan San & Hasan Ali Altunbaş
Akdeniz University Medical Faculty, Antalya, Turkey.

Objective
The frequency of differentiated thyroid cancer in the Graves’ disease are controversial. The aim of this study was to evaluate the frequency of thyroid cancers in patients operated because of Graves’ disease.
Subjects and methods
Sixty-six patients in whom thyroidectomy was performed because of Graves’ disease between 2001 and 2012 were evaluated retrospectively. Patients who had received radioactive iodine treatment and external irradiation treatment in the neck region and who had had thyroid surgery previously were not included in the study.

Results
Thyroid nodule was absent in 17 (25.8%) of 66 Graves’ patients. There was one thyroid nodule in 17 (25.8%) patients, two thyroid nodules in 13 (19.7%) patients, three thyroid nodules in 13 (19.7%) patients, four thyroid nodules in 4 (6.1%) patients, and five and over in 2 (3%) patients. Thirteen (19.7%) patients had thyroid cancer in the s patients. The rate of thyroid cancer was 17.6% (n = 17) in the Graves’ patients who had no nodule, whereas it was statistically not different from other Graves patients with nodules. The risk of thyroid cancer didn’t increased significantly in the presence of nodule.

DOI: 10.1530/endoabs.37.EP917

Association of papillary thyroid cancer with thyroid autoimmunity
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Introduction
Although the association between thyroid autoimmunity and papillary thyroid carcinoma (PTC) is supported by clinical studies, evidence to their pathophysiologic link and causal relationship is lacking. Moreover, there is a paucity of data regarding the association of thyroid autoimmunity with the less common types of differentiated thyroid cancer (DTC). The aim of the current paper was to investigate the association of autoimmune thyroiditis and PTC vs follicular or medullary thyroid cancer.

Methods
We conducted a retrospective, registry-based study in the Department of Endocrinology, Ippokratio General Hospital, Thessaloniki, Greece. Patients with known cancer-related syndromes (patients with autoimmune polyglandular syndrome or multiple endocrine neoplasia) were excluded from the analysis. Thyroid autoimmunity was defined as presence of positive anti-TPO and/or anti-Tg antibodies. Statistical analysis was performed with the use of IBM SPSS 20.

Result
Sixty-five patients with thyroid cancer were assessed (12 men and 53 women). Their mean age was 51 years. Out of 65 patients, 54 patients had PTC, six had follicular carcinoma and five patients had medullary carcinoma. When patients with PTC were compared with patients with follicular or medullary cancer, the prevalence of thyroid autoimmunity was higher in patients with PTC in comparison with patients with other types of thyroid cancer (43% vs 9%, respectively, P = 0.035), independently of TSH concentrations.

Conclusion
This small retrospective study demonstrates that patients with PTC demonstrate significantly higher prevalence of thyroid autoimmunity, in comparison with other types of DTC. Further study into this differential association may provide insights for better prevention and management of PTC.

DOI: 10.1530/endoabs.37.EP918

Primary squamous cell carcinoma of the thyroid: a rare type of thyroid cancer
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Introduction
Primary squamous cell carcinoma (PSCC) of thyroid is a rare type of thyroid malignancies because thyroid gland lacks squamous epithelium. It is seen in <1% of all thyroid malignancies. During last 30 years only about 90 cases were published. PSCC is an aggressive tumour as well as rare.

Case report
We present a 60-year-old female who had been followed up for multiple nodules in thyroid in our outpatient clinic for 2 years. Her serum free thyroxine (fT4), free triiodothyronine (fT3) and TSH levels were 0.9 ng/dl, 1.8 pg/ml, and 3.8 μIU/ml, respectively Her first fine needle aspiration cytology (FNAC) was benign. During follow-up because of sonographic features of nodule in left lobe, we performed the second FNAC which was suspicious for malignancy. Then total thyroidectomy was performed. In histopathological examination, well differentiated squamous cell carcinoma was revealed. Lymphovascular invasion was not seen. After surgery there was no increased glucose metabolism on F-18-fluorodeoxyglucose positron emission tomography. 21 months have passed after surgery and she had no complaint. She is going on the follow-ups.

Conclusion
PSCC of thyroid is rare but aggressive malignancy comparing with other thyroid cancers. FNAC is important for diagnosis like other types. It seems complete surgical eradication of tumour is the main treatment in PSCC of thyroid. But to achieve this, early and accurate diagnosis is important.

DOI: 10.1530/endoabs.37.EP919
EP920
Series of cases a descriptive study of management of metastatic medullary thyroid cancer
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Hospital Virgen del Valle, Seville, Spain.

Introduction
There are new therapies indicated in medullary thyroid cancer (MTC) based on different molecular targets, that appear to be effective in some cases with advanced disease, although many are still under investigation.

Material and methods
We retrospectively evaluated five cases of medullary thyroid advanced carcinoma that later were referred to Oncology Department for Chemotherapy treatment.

Results
Five patients (mean age 52±18.8 years) were evaluated. All cases were sporadic and stage IV at diagnosis. Four cases had undergone total thyroidectomy and cervical lymphadenectomy. three patients had metastases at diagnosis, the other two patients persistent with local disease after surgery. The average value of calcitonin prior to the oncology evaluation was 3072.6±3789.6 pg/ml (382–8600 pg/ml) and CEA 576.5±856.9 ng/ml (13.23–2075 ng/ml). Threeout of five patient received chemotherapy (Vandetanib). The average decrease in calcitonin and CEA in treated patients was 1714ng/ml). None of them showed advanced disease on different imaging studies, and two of them had mild radiological improvement. Two untreated patients had showed a mean increase of calcitonin and CEA of 377 pg/ml and 10.3 ng/ml, in both cases the radiologic stability of the disease remained in time. Only one patient had cutaneous toxicity with Vandetanib.

Conclusions
Patients with Vandetanib had certain laboratory and radiologic improvement, although more investigation of the long-term efficacy would be necessary. In our study, patients with asymptomatic metastatic MTC disease had persisted with radiologic and analytical stability despite not chemotherapy applied. These data are consistent with current recommendations about not to treat patients with these risk factors for incidental PMC in thyroid tissue attached to parathyroid glands.

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EP921
Identification of high-risk patients with incidental papillary microcarcinomas of thyroid helps in deciding appropriate management
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Papillary microcarcinoma (PMC) of thyroid is being increasingly detected following thyroid surgery for various reasons. The management of incidental PMC, not clinically or radiologically evident, is not well defined often leading to over treatment. Identifying risk factors for recurrence could help in administering appropriate management.

Aims and methods
To review the incidence of PMC and management locally. Retrospective review of case notes of patients diagnosed with papillary carcinoma over 9 years (2006–2014).

Results
n = 113, of which 30 were PMC (26.5%). Female = 23. Mean age: 49 years. Lump in the neck was the commonest initial presentation. Patients had one FNAC on an average (Thy3 to Thy5 n = 11). Nine patients with suspicious or diagnostic cytology or non-thyroidal surgeries were excluded. 21 patients had incidental PMC (total thyroidectomy n = 7, lobectomy n = 14). Five patients underwent completion thyroidectomy and further foci of PMC were found in three of them. Eight out of 21 patients were found to have risk factors such as size (6–10 mm), multifocality, and extrathyroidal spread. Five of eight patients had initial total thyroidectomy. Three underwent hemithyroidectomy followed by completion thyroidectomy. Completion thyroidectomy was done in one patient (MEN1) without risk factors for incidental PMC in thyroid tissue attached to parathyroid specimen. Five of 21 patients received radioiodine ablation following surgery (n = 4 with risk factors, n = 1 oncocytic neoplasm). 19 patients received post-operative hormonal therapy including eight with risk factors. TSH level was aimed at 0.1–0.4 mU/l. Complete suppression of TSH was noted at various stages during follow up in four of these 19 patients (21%).

Conclusion
Incidence of PMC in this cohort is in keeping with published literature. Identifying risk factors for local or regional recurrence is helpful in optimising management of incidental PMC. This could avoid unnecessary overtreatment with extensive surgery or RAI ablation or TSH suppression.

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EP922
Incidence of intrathyroid location of parathyroid glands and description of their characteristics compared to extrathyroid ones
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Introduction
Total thyroidectomy (TT) is a safe and effective operation. The most frequent complication after TT is hypoparathyroidism. Surgical trauma, devascularisation of parathyroid glands and inadvertent parathyroidectomy have been identified as the main causes resulting in postoperative hypocalcaemia. The objectives of this study are to investigate the incidence of intrathyroid parathyroid glands (ITPGs) in a large cohort and to clarify their histological characteristics.

Patients and methods
This is a retrospective study of two specialized centers in thyroid diseases. The medical records of patients with thyroidecmy were reviewed. Patients who underwent lobectomy or near total thyroidectomy, intentional parathyroidectomy during TT for concurrent parathyroid diseases, lymph node dissection and patients with inadequate data were excluded from the study. Patients were divided into two groups: those with (P group) and those without parathyroidectomy (non-P group). According to the location of the dissected parathyroid gland the P-group was sub-divided in ITPGs or extrathyroid parathyroid glands (ETPGs). Morphological characteristics of ITPGs were compared with the corresponding characteristics of the ETPGs in a case control way.

Results
4500 patients with TT were included. 605 of them were excluded from the study. Inadvertent parathyroidectomy (IP) was presented in 424 cases (10.89%). Intra-thyroid parathyroid glands were presented in 68 cases (1.75%). There was a trend of ITPGs being smaller in size compared to ETPGs (P = 0.067). Cystic degeneration was presented in ITPGs (P = 0.01). Other histological characteristics, including weight were similar in intra and extra parathyroid glands. Presence of clinical hypocalcaemia was similar in all groups.

Conclusions
The incidence of ITPGs in our cohort is 1.75%. Surgical removal of ITPGs does not increase the presence of clinical hypocalcaemia and should be consider a minor complication of TT. Patients should be informed prior to TT about the possible presence of ITPGs and, therefore, their probable accidental removal.

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Thyroid (non-cancer)

EP923
Histopathological results of suspicious nodules in the patients with Hashimoto thyroiditis
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Endocrine Abstracts (2015) Vol 37
Introduction and aim
The most endocrinologists in routine practice are used to Bethesda classification for evaluation of thyroid nodule in fine needle aspiration biopsy (FNA). It is accepted that FNA biopsy is an accurate diagnostic and gold standard test. However, false-negative diagnosis may sometimes occur as a patient with ‘malign’ lesion is found incorrectly rather than an actually benign lesion on histological examination. Hashimoto’s thyroiditis probably is the most common cause of false-negative cytology. The aims of present study evaluate retrospectively postoperatively biopsy results in patients with Hashimoto disease have a thyroidectomy.

Materials and methods
Results of totally 29 patients with Hashimoto thyroiditis achieved from our hospital records. All of the patients had undergone totally or subtotal thyroidectomy. We re-evaluated retrospectively biopsy results postoperatively. We compared their preoperative FNA results.

Results
We detected 24.1% papillary thyroid cancer in seven patients (mean age 45.5± 11.9 year), 44.8% nodular goitre in 13 patients (mean age 45.8± 4.9 year), 13.7% adenomalous nodule in four patients (mean age 43.5± 14.4 year), 3.4% hurle cell adenoma in one patient with 56 years old. But, 14% in four patients with Hashimoto thyroiditis (mean age 41.5± 13.1 year) were redundantly operated due to atypia of undetermined significance in FNA.

Conclusions
Although Hashimoto disease is a benign diagnosis, its misclassification as atypia of undetermined significance in FNA accounts for some false-positive errors. The cytopathologists can frequently be interpreted as atypia of undetermined significance instead of Hashimoto’s thyroiditis. Therefore, result of atypia of undetermined significance in FNA may lead unnecessarily concern among with the endocrinologists. More importantly, our results demonstrated that high papillary thyroid cancer rate was found postoperatively in suspicious nodules evolved background Hashimoto thyroiditis.

EP924
The evaluation of demographic features and histopathological results in patients with reoperative thyroid surgery
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Introduction
Reoperative surgery for thyroid disease is rare. It is sometimes indicated for nodular recurrence after partial surgery for initially benign thyroid disease or for a completion total thyroidectomy when a final diagnosis of thyroid cancer is confirmed on a permanent section of a partially removed thyroid gland. We aimed to investigate the demographic features and reoperation indications in patients with reoperative thyroidectomy.

Methods
Thirty-six patients reoperated between 2008 and 2011 were included into the study. Demographic features, indications of reoperation and histopathological results of patients were evaluated retrospectively.

Results
After reoperative thyroidectomy, the results of histopathological evaluation of 24 patients were malignant (19 papillary thyroid carcinomas, three follicular thyroid carcinomas, one Hurthle cell neoplasm and one neoplasm with undetermined malignant potential) while 12 patients were benign. Of 36 patients, 11 (30.5%) went to reoperation due to giant thyroid nodule (>4 cm), 5 (13.9%) due to ≥2 non-diagnostic fine needle aspiration biopsy (FNAB), 3 (8.3%) due to toxic multinodular goitre, 5 (13.9%) due to malignant cytology, 2 (5.6%) due to suspected malignancy, 2 (5.6%) due to suspicion for a follicular neoplasm, 3 (8.3%) due to follicular lesion of undetermined significance, 1 (2.8%) due to atypia of undetermined significance, 1 (2.8%) due to suspected Hurthle cell neoplasm and 3 (8.3%) due to cytology of cellular adenomatoid nodule and ultrasonography suggesting malignancy.

Conclusion
Thyroid surgery may lead to regional scars and some degree of fibrotic process. This may result in problems in collecting thyroid FNAB samples and assessing cellular abnormalities. Our study findings demonstrated that histopathological evaluation of 14 patients whose cytological results showed no malignancy, was consistent with malignancy. We consider that decision for reoperative thyroidectomy should not be made with cytological findings, but patients’ symptoms and ultrasound findings should also be taken into account.

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EP925
A case of primary hypothyroidism initially presenting with massive pericardial effusion
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Introduction
Although pericardial effusion is a common finding in primary hypothyroidism, massive pericardial effusion diagnosed by Echocardiography and ejection fraction was measured 57%. Pericardiocentesis was not performed because of a total of 2800 cc of fluid was evacuated. Complete blood count, routine biochemical tests and erythrocyte sedimentation rate were normal. No bacterial growth was observed in pericardial fluid samples and cytological examination revealed no findings suggesting malignancy. Also, adenine deaminase level was normal and no growth occurred in Lowenstein-Jensen medium. Rheumatoid factor, anti-nuclear antibody profile, and viral markers (HIV and HBsAg) were negative. Thyroid function tests were as follows: TSH > 150 mIU/L (n: 0.5–4.7), fT3 0.2 ng/dl (n: 0.8–1.7), fT4 1.2 µg/ml (n: 1.8–4.6 µg/ml), antiTPO and antiTG negative. There were no findings in ultrasound examination of the thyroid gland. Consequently, a diagnosis of primary hypothyroidism was made and replacement treatment was initiated with 50 µg/day of levothyroxine with gradual dose titration. Follow-up examination after 6 months was normal and no pericardial effusion detected by echocardiography.

Conclusion
Massive pericardial effusion is a rare complication of hypothyroidism and patients frequently exhibit other signs and symptoms of hypothyroid before the development of pericardial effusion. However, in the patient described herein, initial presentation involved massive pericardial effusion associated with dyspnea. Physicians should keep in their mind that massive pericardial effusion might precede overt symptoms of hypothyroidism.

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EP926
Usefulness of Body Adiposity Index % in comparison to body composition analyser parameters among patients with and without autoimmune thyroid diseases hospitalised on Endocrinology
Department-preliminary report
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Usefulness of Body Adiposity Index % in comparison to body composition analyser parameters among patients with and without autoimmune thyroid diseases hospitalised on Endocrinology

Department-preliminary report

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Endocrine Abstracts (2015) Vol 37
Introduction
Anthropometric parameters such like BMI aren’t suitable enough for each type of figure and leads to misinformation about body composition. Body Adiposity Index (BAI) is suggested as an alternative for BMI.

Aim
The aim of the study was to compare the usefulness of BAI in context to body composition parameters.

Materials and methods
The BAI index was calculated for 86 patients according to previously described formula. The patients were divided into three examined groups: autoimmune thyroid disorders (including Hashimoto disease, Graves Basedow disease) (AITD) (n=40), non autoimunological diseases of thyroid gland like thyroid goiter (non AITD) (n=16), and controls without thyroid dysfunction (n=30).

The body analysis was done in the morning in light clothes by specialist equipment with Medical Device Directive. Spearman’s rank correlation was used. The collected data were statistically analysed, α=0.05.

Results
The mean age in group with autoimmune thyroid diseases AITD was 46.5±15.97, BAI 34.33±7.29%, the mean of age in group with non autoimunological diseases was 43.75±17.81, BAI 34.03±6.25% among patients without thyroid diseases the mean age was 28.17±9.76, BAI 30.38±5.22%. In each group BAI correlates with parameters obtained from body analyzer. Strong positive correlation was observed between BAI and % amount of body fat in group of females. We observed considerably higher fT4 and lower fT3 levels in LT4 users, the largest reduction was observed in physical functioning, bodily pain, and general health and vitality. In the non-users, those in the lowest tertile of the fT3/fT4-ratio reported a significantly lower HR-QOL, in the domains physical functioning, bodily pain, and general health compared to participants in the middle and highest tertile.

Conclusion
Patients treated with LT4 monotherapy for primary hypothyroidism report low HR-QOL. In subjects not using LT4, a lower fT3/fT4-ratio was associated with more impairments in HR-QOL.

Disclosure
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EP928
Assessment of vitamin D (25-OH vitamin D3) concentration among patients with and without autoimmune thyroid diseases hospitalised on Endocrinology Department-preliminary report
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Aim
To assess the concentrations of vitamin D as well as antiTPO level among patients with thyroid dysfunction hospitalised on Endocrinology Department.

Materials and methods
The study was conducted among 86 patients, which were divided into three groups: Autoimmune Thyroid Disorders AITD (including Hashimoto disease, Graves Basedow disease) (n=40), non autoimunological diseases of thyroid gland (e.g. thyroid goitre) (n=16), and persons without thyroid dysfunction (n=30) as control group. The Kruscal Wallis test and Spearman rank correlation were used. The collected data were statistically analysed, α=0.05.

Results
The mean age in group with autoimmune thyroid diseases AITD was 46.5±15.9, mean of age in group with non autoimunological diseases was 43.75±17.81, antiTPO 0.63±1 IU/ml, vitamin D 18.3±7.42 ng/ml and among patients without thyroid diseases the mean age was 28.17±9.78 and antiTPO 0.57±0.98 IU/ml, vitamin D 16.54±5.51 ng/ml. The statistical significance difference was observed between groups according to age (P=0.0000) and antiTPO level (P=0.0000), the statistical difference wasn’t observed between vitamin D concentration in analysed groups. In all group of 86 patients positive correlation between age and antiTPO level was observed (P=0.00003). Obesity was most frequently observed among patients with AITD. The vitamin D deficiency defined as level below 20 ng/ml was observed among 71% of all of hospitalised patients.

Conclusions
Screening of thyroid function should be done among patients with overweight, obesity and also among patients over 40. Vitamin D deficiencies should be diagnosed and corrected according to guidelines recommended in Central Europe.

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EP929

Renal involvement in Graves’ disease patients treated with Benzylthiourea

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Introduction

Renal complications in Graves’ disease are rare and may be related either to the disease itself or secondary to antithyroid drugs.

Methods

We report seven cases of renal damage in patients with Graves’ disease treated with Benzylthiourea collected over a period of 14 years.

Results

There were seven women with a mean age of 37.86 ± 14.25 years (19–61 years). Six patients developed renal vasculitis associated with ANCA. The signs were dominated by renal proteinuria and renal failure noted in all cases and associated with hematuria in five cases. The lung involvement was the most common extrarenal manifestation occurred in four patients (alveolar hemorrhage in two cases, lymphocytic alveolitis in one case and pleurisy in 1 case). The benzylthiourea was discontinued in four patients still under treatment. Corticosteroid therapy was used alone or in combination with cyclophosphamide in all cases. Phlebopheresis sessions were made during the alveolar hemorrhage. A complete remission was obtained in one case and incomplete remission in two cases. The other three patients required chronic hemodialysis. One patient died of sepsis. The seventh patient developed a nephrotic syndrome and was treated with corticosteroids.

Conclusion

The possibility of renal impairment in Graves’ disease requires monitoring to detect urinary abnormalities in order to early initiate therapy and improve patient’s outcome.

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EP930

Indications and outcomes of repeated thyroid fine-needle aspirations: a retrospective evaluation from a tertiary centre

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Introduction

Fine needle aspiration (FNA) is the first-line diagnostic test for evaluating thyroid nodules. This test can effectively distinguish between neoplastic and non neoplastic nodules. The Bethesda System suggest that thyroid nodules with non diagnostic (ND), atypia/follicular lesions of undetermined significance (A/FLUS) aspiration should undergo repeat sampling. We aimed to investigate the clinical validity of repeated FNA in the management of patients with thyroid nodules in our institution.

Methods/design

In this study we evaluated 688 nodules of 529 patients who underwent repeated sampling in Başkent University Hospital between 2000 and 2014.

Results

The majority of patients were female (n=421, %79.6). The mean age of patients was 60.1 ± 14.5 years. First evaluation revealed that 467 (89.9%) of nodules were benign, 180 (26.9%) were non diagnostic and 21 (3.1%) were A/FLUS. Enlargement of the nodule (%27.9) was the most common indication for a repeated sampling followed by non-diagnostic cytology (%36.9). Re-aspiration altered the initial diagnosis in 84.4% and 66.7% of the non-diagnostic and A/FLUS patients but only in 10.7% of patients with a benign cytology the initial diagnosis was changed. We evaluated the outcome of patients whose initial and repeated cytological diagnosis are non diagnostic and A/FLUS (Table 1). Outcome data was obtained 23 (65.7%) of these patients.

Conclusion

Repeat FNA is useful in cases whose initial diagnosis is non diagnostic or A/FLUS, but repeated aspiration for patients with an initial benign examination appears to not increase the expected likelihood of a malignant cytology.

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EP931

The efficacy of radiiodine therapy in patients with non-toxic nodular goitre with large cold nodule

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Most of the patients with the benign cold nodule refuse surgical operation. Radiodine therapy (RIT) is the choice for these patients. The aim of our study was to evaluate the efficacy of radiiodine therapy to reduce thyroid volume in patients with cold nodule by the use of two doses of radiodine.

Methods

We treated 40 patients with non-toxic nodular goitre with large cold nodule, aged 18 and 48 years; initial 24 h radiodine uptake (RAIU) was ranged between 18–45%, and thyroid volume ranged between 48 and 120 ml, effective half-life was more than 3 days at the time of treatment. Malignant changes were excluded in all nodules by fine needle aspiration biopsy. The activity dose was calculated by the use of Marinnelli’s formula and ranged between 280 and 800 MBq. Thyroid ultrasonography, and thyroid scan with RAIU at 24 was done before and after 6 and 12 months of RIT. Follow up control was done every 6 weeks.

Results

After 6 months RIT in all the patients the large cold nodule changes to hot nodule. In 13 patients the size of the thyroid gland decrease to 48%, and no need for the second dose of radiodine therapy. 27 patients received second dose of RIT to decrease the nodule which was cold and turned to hot after the first dose. After 12 months of the second dose of radiodine a mean thyroid volume reduction of 56% was achieved. After 12 months of RIT euthyroidism persist in 52% of patients, and hypothyroidism develop in 48% of patients.

Conclusions

Radioiodine is non-invasive, safe and cost effective method of therapy for reduction of large non-toxic goitre even with cold nodule. The reduction of the cold nodule and the thyroid volume, were due to well accurate measurement of administered activity, relatively high effective half-life and well-organised follow up.

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EP932

Fibromyalgia in patients with euthyroid Hashimoto’s thyroiditis

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Introduction

The aims of this study are to evaluate fibromyalgia (FM) in patients with euthyroid Hashimoto’s thyroiditis (HT) and whether antithyroperoxidase antibody (TPOab) positivity is associated with the FM.

Methods

We have studied 167 patients with HT and 83 healthy controls followed in our hospital. Single researcher took the history and did physical examination including manual tender point examination according to Manual Tender Point Survey instructions. For the diagnosis FM, 2010 American College of Rheumatology Classification Criteria for the FM was used. Thyroid assessment was done by free T4, free T3, TSH, antithyroglobulin antibody (TgAb) and TPOab. Patients were excluded from the study if they had any other serious disease, and if there was any history of drug use that interferes with the symptoms of FM.

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FM was found in 40% (67 out of 167 patients) of HT patients, in 7% (six out of 83 healthy controls, P < 0.001) of controls. The average age was significantly higher in patients with FM than controls (43.78 ± 10.48 years vs 40.43 ± 10.52 years, P = 0.02). TSH (2.97 ± 2.03 vs 2.20 ± 1.33, P = 0.001), TPOAb (240.92 ± 268.6 vs 197.05 ± 288.14, P = 0.006) and TgAb levels (300.68 ± 528.79 vs 153.76 ± 411.51, P = 0.003) were significantly higher in patients with FM, according to patients without FM. Widespread pain index, symptom severity scale and tender point examination showed no significant difference between the patient and control group. On the other hand widespread pain index, symptom severity scale and tender point examination showed a positive correlation with TSH (r = 0.184, r = 0.004; r = 0.204, P < 0.001; r = 0.167, P = 0.009; respectively). Also TgAb showed positive correlation with symptom severity scale (r = 0.168, P = 0.02). Increasing age in patients with HT showed positive relationship with widespread pain index and tender point examination(r = 0.193, P = 0.012 and r = 0.170, P = 0.02 respectively).

Conclusion
In our study, euthyroid HT patients showed significantly higher prevalence of FM, as compared to healthy control. This finding support thyroid autoimmunity may influence the development of FM, but the evidence which support that FM is related to autoimmune aetiology is not clear, and FM severity may not be affected by the presence of thyroid autoantibody.

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False positive post RAI scan in a subject with papillary thyroid cancer secondary to urine contamination
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Introduction
Radioactive iodine (RAI) for remnant ablation and post RAI scanning are very frequently employed modalities in differentiated thyroid cancers (DTC). Radioactive iodine is secreted into physiological secretions such as tears and urine. In this case report we present a case who received RAI for DTC with a surprising post RAI scan compatible with multiple metastases.

Case report
A 53-year-old male subject underwent total thyroidectomy and ipsilateral lymph node dissection after being diagnosed as papillary thyroid cancer (PTC) via fine needle aspiration cytology (FNAC). He received 150 mCi of RAI due to lymph node metastases. His stimulated thyroglobulin level (Tg) was 33.3 ng/ml and was positive for anti thyroglobulin antibodies. In the post RAI scan we visualized suspicious metastases in the thyroid area together with the mid abdominal, proximal right femoral, mid left femoral and distal left tibia areas. The metastatic findings were untypical and were localized anteriorly. Also the patients’ general situation was fine so we planned a bone scan and PET CT to confirm these findings were untypical and were localized anteriorly. Also the patients’ general situation was fine so we planned a bone scan and PET CT to confirm these findings were untypical and were localized anteriorly. Also the patients’ general situation was fine so we planned a bone scan and PET CT to confirm these findings were untypical and were localized anteriorly. Also the patients’ general situation was fine so we planned a bone scan and PET CT to confirm these findings were untypical and were localized anteriorly. Also the patients’ general situation was fine so we planned a bone scan and PET CT to confirm these findings were untypical and were localized anteriorly. Also the patients’ general situation was fine so we planned a bone scan and PET CT to confirm these findings were untypical and were localized anteriorly. Also the patients’ general situation was fine so we planned a bone scan and PET CT to confirm these findings were untypical and were localized anteriorly. Also the patients’ general situation was fine so we planned a bone scan and PET CT to confirm these findings were untypical and were localized anteriorly. Also the patients’ general situation was fine so we planned a bone scan and PET CT to confirm these findings were untypical and were localized anteriorly.

Discussion
Post RAI scanning is a very important technique for determining metastases in subjects with DTC. Contamination with body fluids can cause false metastatic findings in which other radiological methods and personal history can aid the physicians in making a decision.

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Smoking associated with TSH receptor antibody and serum IL17A elevation in hyperthyroid Graves’ disease
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Th17 cells represent newly discovered CD4+ T cells producing predominantly IL17A cytokines, which are involved in inflammations and autoimmune diseases. Elevated IL17 levels were demonstrated in thyroid autoimmunity and the activity of Graves’ ophthalmopathy. The relationship among IL17A, anti-thyroid antibodies, smoking, and clinical activity score of ophthalmopathy was investigated in hyperthyroid Graves’ disease. One hundred and thirty-eight patients, 62 with Graves’ disease (25 with ophthalmopathy, 33 with hyperthyroidism, and 17 have daily smoking), 38 with Hashimoto’s thyroiditis and 38 healthy controls were investigated. Serum IL17A levels were measured with ELISA; thyroid hormones, anti-thyroid antibodies in a fully automated way, but TSH receptor antibodies with RIA. IL17A serum levels were higher in Graves’ patients than those in Hashimoto’s thyrotoxics and controls (5.28 ± 5.8 with or 5.43 ± 3.62 ng/ml without ophthalmopathy vs 3.65 ± 2.22 ng/ml, P < 0.04 or P < 0.01, respectively, for Hashimoto’s thyrotoxics and vs 2.83 ± 0.73 ng/ml, P < 0.0001 and 0.004 respectively for controls). Smoking increased IL17A levels in comparison with nonsmoking patients in hyperthyroid Graves’ patients after thyrotropic therapy (2.90 ± 1.44 ng/ml vs 10.46 ± 7.18 ng/ml, P < 0.004). TSH receptor antibody positive and hyperthyroid smoking patients showed significantly higher IL17A and TSH receptor antibody levels than those who were nonsmoking (3.59 ± 2.28 ng/ml vs 7.24 ± 5.42 ng/ml, P < 0.02 for IL17A and 9.07 ± 9.39 IU/l vs 22.52 ± 11.48 IU/l, P < 0.01 for TSH receptor antibodies). No relevant elevation in IL17A levels was connected to clinical activity score of ophthalmopathy. The results highlight the role of IL17A levels in hyperthyroid Graves’ disease. Smoking can play as an aggravating factor in IL17A and TSH receptor antibody elevation.

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Evaluation of acoustic voice analysis in patients with subclinical thyrotoxicosis
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Introduction
The relationship between hyperthyroidism and voice disorders has not been identified before. The aim of this study was to investigate the changes in the acoustic values in patients with subclinical thyrotoxicosis.

Methods
In this study, acoustic voice analysis was evaluated in a total of 115 cases. Sixty of 115 individuals (18 men and 42 women) had subclinical thyrotoxicosis, aged between 18 and 65 years, and all had no history of laryngeal surgery, no vocal complaints. These patients were compared with the control group consisting of 55 cases (18 men and 37 women) with similar characteristics. Acoustic and perceptual analyses are the most commonly used method in the assessment of voice quality. Kay CSL 4300 unit was used for acoustic voice analysis and as the operating parameters, F0 (fundamental frequency), Jitter, Rap (relative average perturbation), Shimmer, noise-to-harmonic ratio (NHR), and voice turbulence index (VTI) values were evaluated. The results were evaluated using the Mann–Whitney U statistical method.

Results
The performed acoustic analysis showed that mean values of the investigated parameters in patients were Jitter (%) 1.18, Shimmer (%) 4.00, Rap (%) 0.70, F0 (Hz) 207.86, VTI 0.05, and NHR (dB) 0.12. There was no statistically significant difference between the control group and patients (P<0.05).

Conclusions
In our study, it was concluded that the moderate increase in thyroid hormones doesn’t affect the voice quality. Effect on the voice quality of the excess of thyroid hormones, such as clinical thyrotoxicosis was not evaluated. Therefore, further studies are needed to interpret the relationship between thyroid hormone and voice quality.

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EP936

Transient pulmonary hypertension in patients with Graves’ disease
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Introduction

Hyperthyroidism produces changes in cardiac contractility, blood pressure, and systemic or pulmonary vascular resistance. In almost all cases these cardiovascular changes are reversible when the underlying thyroid disorder is recognized and treated. Pulmonary hypertension (PH) has been associated with thyroid dysfunction, but primarily with hyperthyroidism. The vast majority of patients with this form of PAH are usually older with toxic multinodular goitre. The aim of this study was to determine the clinical correlates of PAH in patients with Graves’ disease (GD).

Methods

Our study is retrospective one concerning patients with GD referred for echocardiography before using any treatment. PAH has been diagnosed when pulmonary systolic pressure was elevated. Results

Among 22 consecutive patients with GD referred for echocardiography, six patients (27.22%) had PAH measured by continuous-wave Doppler echocardiography (pulmonary artery systolic pressure > 35 mmHg). The patients with PAH had significantly higher pulmonary vascular resistance (PVR), cardiac output, and TSH receptor antibody (TRAb) compared to those without. Pulmonary artery systolic pressure may had a good correlation with TRAb, but was not related to free T3. All the patients have a reversible pulmonary hypertension after treatment.

Discussion

In addition to the effect of thyroid hormone on the cardiovascular system, autoimmune-mediated pulmonary vascular remodelling may play a role in Graves’ disease-linked elevated pulmonary artery systolic pressure. An autoimmune process inducing endothelial damage with GD may play a key role. Future studies should focus on discovering the immunogenetic overlap between autoimmune thyroid diseases and PAH.

Conclusion

Study highlights the importance of considering hyperthyroidism as a cause of idiopathic PAH, and demonstrates the potential reversibility of its complications. At present, thyroid function tests should be considered in the investigation of all patients.

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EP937

Side effects of steroid therapy in Graves’ orbitopathy: comparison of two different protocols: parenteral vs combined parenteral and oral
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Introduction

Glucocorticoids (GCs) are the treatment of choice for moderate-to-severe and active Graves’ orbitopathy (GO), but optimal treatment is still undefined as serious side effects are great concern of GC therapy. The aim of the present study was to evaluate tolerability and safety of two different treatment protocols.

Methods

Consecutive patients were divided according to the protocol of GC therapy into two groups: combined intravenous and oral GC therapy (combined GC group, 66 patients, 49 ± 10 years), and only intravenous GC therapy (IVGC group, 66 patients, 50 ± 11 years, P = NS). Combined GC therapy included 500 mg of methylprednisolone in 500 ml of saline solution for 2 alternative days, followed by oral prednisone tapering dose that was repeated each month for the next 5 months. Cumulative dose was 10.2 g. IVGC therapy included infusions of 500 mg of methylprednisolone for the first 6 weeks, and then infusions of 250 mg for the remaining 6 weeks. Cumulative dose was 4.5 g.

Results

Combined GC therapy induced significantly more side effects in comparison to IVGC (49 ± 6 years, 74% vs 28%, 42%, P < 0.001), including weight gain of > 3 kg (55% vs 22%, P < 0.001), hirsuitism in female patients (49% vs 4%, P < 0.001), myalgias (33% vs 0%, P < 0.001), sleeplessness (17% vs 2%, P = 0.004), and urinary infections (15% vs 3%, P = 0.03). Increase in total cholesterol (42% vs 35%) and development of diabetes (8% vs 3%) was also more prevalent without reaching statistical significance (P = NS). Considering serious side effects two patients in combined GC group developed herpes zoster infection and pulmonary tuberculosis, whereas one patient in IVGC group had myocardial infarction during IVGC therapy.

Conclusion

Side effects were more prevalent in the combined group, as a consequence of higher cumulative dose, longer duration of therapy (6 months vs 3 months), and treatment schedule. Careful monitoring during GC therapy in patients with GO is mandatory in both treatment protocols.

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EP938

Isolated cutaneous findings of systemic lupus erythematosus due to propylthiouracil
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Propylthiouracil (PTU), used to treat thyroid dysfunctions such as Graves’ disease, rarely induces lupus-like syndrome. A 52-year-old woman developed dermatological findings of systemic lupus erythematosus with malar rash, photosensitivity and discoid lupus erythematosus-like lesions, after 3 weeks of exposure to the drug. ANA and anti-dsDNA were positive. Skin biopsy of face revealed vacuolar changes in basal layer and lymphoid infiltration in perivascular region of dermis. No other organ involvement was diagnosed. PTU treatment was stopped and oral prednisolone 40 mg daily, in 3 weeks she had resolution of lesions. The patient has no skin lesions in 2-month follow-up. This is a report of isolated skin findings of lupus-like syndrome with positive serologies and without any other organ involvement. The physicians should be aware of this rare but potentially serious, possible adverse effect of PTU.

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EP939

Seasonality in paediatric Graves’ disease compared to the general population: impact of month of birth: a national study
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Paediatric Graves’ disease (PGD) is an uncommon autoimmune disorder with a multifactorial origin. Although, in some autoimmune endocrinopathies the seasonality of month of birth (MOB) distribution differed from the general population, this association has not been study in PGD. The aim of this work was to analyse the impact of seasonality of MOB on PGD incidence in Portugal. In 2013, the Portuguese Paediatric Society of Diabetes and Endocrinology undertook a national multicentric study of the PGD (153 cases). We compared the distribution of MOB within this study with the Portuguese population (data from the National Institute of Statistics). Since, the mean age at diagnosis was 11 years, we restricted the study period up to 2001 to correct for that variation (125 cases). Statistical analysis was performed with STATA Software, version 12.0. Walter and Elwood method was used because it takes into account the population at risk. A total of 125 cases of PGD born between 1983 and 2001 were recorded (75% females) compared to 2 271 523 births (49% females). Among PGD, the percentage of observed to expected births did not differ across the 12 months (P = 0.7). Nevertheless, the smoothed birth-month estimates demonstrated a non-significant (NS) excess of births from September to April, and a deficit from May to July. The evaluation of the subgroup with higher TRABS titers at diagnosis (50 cases with TRABS ten times the upper limit of normal), did not show a higher incidence compared to the Portuguese population (P = 0.7).

This was the first population-based study that analysed the impact of seasonality of MOB in the incidence of PGD. Despite a trend to a higher incidence of PGD in children born between September and April, no uniform seasonal pattern of MOB in PGD was observed in this sample of the Portuguese population. We thank the Portuguese Paediatric Society of Diabetes and Endocrinology for allowing the study data to be used in this work.

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**EP940**

Late onset of amiodarone-induced thyrotoxicosis causing pharmacoresistant atrial fibrillation with subsequent development of serious heart failure

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Amiodarone is a potent and among cardiologists still very popular anti-arrhythmic drug. This case report describes severe course of amiodarone-induced thyrotoxicosis (AIT) which is one of the most serious side effects of the treatment. The patient (J.S. born in 1950) was first hospitalised in June 2012 for atrial fibrillation with rapid ventricular response and tachycardia-induced cardiomyopathy with a decreased ejection fraction (EF). Thyroid hormones were normal at that time and electric cardioversion was successfully performed and following echocardiography showed improving EF. Attending cardiologist added to the medication amiodarone which was after <6 months discontinued for symptomatic corneal deposits. The second hospitalisation for the same reason was in September 2013. According to laboratory findings, ultrasonography and scintigraphy we diagnosed a destructive type of amiodarone-induced thyrotoxicosis more than half a year after the withdrawal of this drug! We started treatment with combined antithyroid medication at higher doses (including parenteral forms of administration) and corticosteroids. The atrial fibrillation was resistant to standard doses of β-blockers even in combination with digoxin. However, despite the normalisation of thyroid hormones the patient had to be after 33 days of treatment moved to ICU with a serious heart failure. After administration of levosimendan, diuretics and after an electric cardioversion was carried out, the clinical condition began to improve. We had decided for a total thyroidectomy and afterwards we started a substitution therapy with levothyroxine. Recurrence of atrial fibrillation in October 2014 was without any major concern quickly solved by pharmacological cardioversion with amiodarone. Nowadays, the amiodarone treatment was discontinued, the patient keeps sinus rhythm and in future a fibrillation ablation is planned. This case report draws attention to the risk of developing a serious AIT even after a long time since discontinuation of administering amiodarone.

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**EP942**

The evaluation of TSH-receptor antibody in hyperthyroid patients treated with surgery or radioactive iodine

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Introduction

Radioactive iodine (RAI) therapy is widely used in the treatment of hyperthyroidism especially in patients with Graves’ disease (GD), toxic multinodular goitre (TMNG), and toxic adenoma. RAI may lead to worsening of the autoimmunity with the elevation of TSH-receptor antibody (TRAB). In this study, we aimed to compare the effects of surgery or RAI treatment on TRAB.

Methods

Hyperthyroid patients were divided into three groups; patients in group 1 (n = 23) had GD conducted to RAI, in group 2 (n = 18) had TMNG referred to RAI, and group 3 (n = 12) had GD who underwent to surgery. Before and 12 months after RAI and surgery, sera were collected and analysed for the presence of TRAB.

Results

In group 1, there were eight patients (34.8%) before treatment and 14 patients after treatment with TRAB positivity (P = 0.311). In group 2, before treatment there were two patients (11.1%) with TRAB positivity, whereas after treatment there were four patients (22.2%) (P = 0.423). In group 3, TRAB positivity were in six patients (50%) and in one patient (8.3%) before and after treatment respectively (P = 0.296). However, there was no difference in TRAB positivity between groups 1 and 3 before treatment (P = 0.383), TRAB positivity was statistically higher in group 1 than group 3 at 12 months of treatment (P = 0.003). There was no difference between groups 1 and 2 before treatment (P = 0.080). TRAB positivity was significantly higher in group 1 than group 2 at 12 months of treatment (P = 0.013).

Conclusion

RAI treatment can induce autoimmunity in patients with TMNG similar as in patients with GD. We observed similar ratios of TRAB positivity in patients with GD and TMNG before and 12 months after treatment. Whereas 12 months after the treatment, we demonstrated higher TRAB titres in GD patients treated with RAI than underwent to surgery.

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**EP943**

Dynamic thiol/disulphide homeostasis in patients with autoimmune subclinical hypothyroidism

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Objective

To investigate dynamic thiol/disulphide homeostasis in autoimmune subclinical hypothyroidism.

Materials and methods

48 patients with newly diagnosed subclinical hypothyroidism due to Hashimoto’s thyroiditis and not yet on any treatment and 48 healthy subjects without any known disease were enrolled. Thiol/disulphide homeostasis (native thiol(SH)–disulphide(S–S) exchanges) was measured in both groups with new method developed by Erel and Neselioglu. The half of the difference between total thiol ((SH + S–S)) and -SH concentrations gave the S–S bond amount.

In patients with subclinical hypothyroidism, -SH level and -SH/(SH+S–S) ratio was found to be lower than that of the control group. -SH level (P = 0.004),

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Erel and Neselioglu.

autoantibody levels. The efficacy, dose and duration of thiol drugs may be consequence, may be illustrated by using thiol-containing drugs and following were correlated positively with thiol oxidation. Abnormal thiol/disulfide homeostasis in patients with Hashimoto’s thyroiditis, is whether a cause or a consequence, may be illustrated by using thiol-containing drugs and following autoantibody levels. The efficacy, dose and duration of thiol drugs may be monitored easily, effectively, quickly and cheaply by the method developed by Erel and Neselioglu.

Conclusions

Disulfide homeostasis was found to have a tendency towards -S-S- on patients with Hashimoto’s thyroiditis, whether a cause or a consequence, may be illustrated by using thiol-containing drugs and following autoantibody levels. The efficacy, dose and duration of thiol drugs may be monitored easily, effectively, quickly and cheaply by the method developed by Erel and Neselioglu.


EP944

Is oxidative stress an effective risk factor in the development of overt hypothyroidism in Hashimoto’s thyroiditis?

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Objective

We aimed to investigate the effects of oxidative stress in the pathogenesis and progression of thyroiditis in patients with Hashimoto’s thyroiditis whose aetopathogenesis includes environmental and genetic factors.

Methods

80 patients (40 euthyroid and 40 subclinical hypothyroidism) older than 18 years with newly diagnosed Hashimoto’s thyroiditis and not yet on any treatment were enrolled. Patients were followed up for 9 months. Blood sample was drawn at diagnosis for thyroid function tests and oxidative stress parameters. Total antioxidant status (TAS), total oxidative status (TOS), paraoxonase 1 (PON1), arylesterase, and total thiol (total SH) were measured by colorimetric method. The ratio of serum TOS level and TAS level gave the oxidative stress index. TSH, free thyroxine (fT 4), anti-thyroid peroxidase (anti-TPO), and anti-thyroglobulin (anti-Tg) were measured by ECLIJA method.

Results

Total SH level was found to be higher in the euthyroid group as compared to the subclinical hypothyroidism group (P =0.019). TAS, TOS, OSI, PON, and arylesterase levels were similar in the two groups (P >0.05). At 9 months of follow-up, overt hypothyroidism developed in 14 patients. Patients with overt hypothyroidism tended to have significantly higher average TOS and OSI levels at diagnosis (P <0.001) and significantly higher anti-Tg and anti-TPO levels at hypothyroidism development (P <0.05) than those who did not develop overt hypothyroidism. Multivariable Cox regression analysis showed TSH level (HR = 1.348, P <0.001), fT 4 level (HR = 0.981, P =0.017), and OSI ratio (HR = 2.349, P =0.001) to be independent predictors for the development of overt hypothyroidism in euthyroid patients and those with subclinical hypothyroidism.

Conclusion

Higher levels of autoantibodies and oxidative stress in patients developing overt hypothyroidism shows that oxidative stress plays a major role in the pathogenesis and progression of autoimmune thyroiditis.

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EP945

Does treatment with levothyroxine sodium decrease oxidative stress in Hashimoto’s thyroiditis?

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Background

In Hashimoto’s thyroiditis, chronic inflammation and autoimmunity increases oxidant radicals and cause oxidative stress. However, the effect of levothyroxine therapy on the oxidant and antioxidant systems is not known in overt hypothyroidism. Therefore, we sought to investigate the effect of levothyroxine sodium therapy on oxidative stress in patients with Hashimoto thyroiditis and overt hypothyroidism.

Materials and methods

36 patients (nine males and 27 females) with a diagnosis of Hashimoto’s thyroiditis and overt hypothyroidism older than 18 years and not yet on any therapy were enrolled. Blood samples were taken at diagnosis and after 6 months following treatment with levothyroxine for measurement of TSH, free thyroxine (fT 4), anti-thyroid peroxidase (anti-TPO), anti-thyroglobulin (anti-Tg), and oxidative stress parameters. TSH, fT 4, anti-TPO, and anti-Tg levels were measured using the ECLIJA method. Total antioxidant status (TAS), total oxidative status (TOS), paraoxonase 1 (PON1), arylesterase, and total thiol (total SH) levels were measured using the colorimetric method. Oxidative stress index (OSI) was obtained from the ratio of TOS and TAS levels.

Results

TSH, anti-TPO, and anti-Tg levels decreased after treatment (P <0.05) while fT 4 level increased (P <0.05). TAS level increased after treatment (1.5±0.2 vs 1.7±0.3, P =0.030) while TOS level decreased (6.5±1.9 vs 4.4±1.3, P =0.012). OSI ratio also decreased after treatment (4.3±2.3 vs 2.7±1, P =0.003). Total SH level increased after treatment (442.8±63.8 vs 470.3±30.1, P =0.034), but no significant change was observed in arylesterase and log(PON) levels.

Conclusion

Levothyroxine treatment was found to have positive effects in terms of thyroid antibodies and oxidative stress parameters in patients with Hashimoto’s thyroiditis. More studies are needed to understand whether this effect of levothyroxine is due to increase of antioxidant molecules and induction of enzyme synthesis or reduction of inflammation.


EP946

Concomitant Graves’ disease and primary hyperparathyroidism: case report

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Introduction

Hyperthyroidism is associated with asymptomatic hypercalcaemia due to increased calcium mobilization from bone and catecholamine metabolism. Hypercalcaemia secondary to hyperthyroidism coexists with decreased or normal parathyroid hormone level. We reported case of 30-year-old man who suffered from Graves’ disease and primary hyperparathyroidism.

Case report

A 30-year-old male patient was admitted to our hospital suffered from palpitation, heat intolerance and sweating. He had blood pressure of 130/90 mmHg, heart rate of 102 beats/min, and temperature of 36.6 °C. He had warm and moist skin. Blood tests showed TSH <0.03 μU/l, fT 3 14.34 pg/ml, and fT 4 3.91 pg/ml. Other results: anti-TPO 229 IU/ml, TRAbs 0.73 U/l, serum calcium 11.05 mg/dl, and 24-h collected urine showed creatinine clearance of 132 ml/min and calcium excretion of 428 mg/day. Other laboratory parameters were largely within normal ranges. Ultrasonography revealed enlarged thyroid gland with inhomogeneous pattern. Scintigraphy of the thyroid gland was consistent with Graves’ disease. Scintigraphy of the parathyroid glands revealed parathyroid adenoma. Patient was treated with propylthiouracil 300 mg/day and propranolol 20 mg twice a day. Treatment successfully controlled sympathetic symptoms. When he became euthyroid, serum calcium, and parathyroid hormone was still elevated. Subtotal thyroidectomy and parathyroidectomy was performed. The follow-up investigations showed normalisation of serum calcium and parathyroid hormone.

Conclusion

Constant hypercalcaemia after treatment of hyperthyroidism may indicate concomitant hyperparathyroidism if iPTH level is not reduced. It should be considered that, slightly or moderately elevated iPTH levels in hypercalcaemia coexists with hyperthyroidism, may suggest hyperparathyroidism. Ultrasonography, scintigraphy, and ultrasound guided fine-needle biopsy of parathyroid
gland lesions can be used for differential diagnosis. Avoiding from repeated operations and complications; the best treatment is combined resection of thyroid and parathyroid gland when concomitant parathyroid adenoma is determined. DOI: 10.1530/endoabs.37.EP946

**EP947**
Measurement of epicardial adipose tissue (EAT) thickness in subclinical hypothyroid patients and to determine the relationship between EAT and abdominal/visceral fat mass
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Background
Subclinical hypothyroidism (SH) is defined as high TSH accompanied with normal free thyroxine (fT3). SH has been found to be associated with cardiovascular disease (CVD) and increased mortality. Epicardial adipose tissue (EAT) is now considered to be a new non-invasive measurement method used for the early detection of CVD susceptibility. EAT has vasodilatory and paracrine actions which lead to CVD. We aimed to evaluate measurement of EAT and to detect relationship between EAT and abdominal/visceral fat mass in patients with SH. Material and methods
This study included 41 patients with SH and 35 healthy controls (matched in age and gender). Demographic data (age, gender, BMI, fat mass (FM), abdominal FM, visceral FM, waist circumference (WC), hip circumferences (HC), systolic and diastolic blood pressure) and laboratory results (fasting plasma glucose (FPG), LDL cholesterol (LDL-c), HDL cholesterol (HDL-C), triglycerides (TGs), fT3, TSH, and anti-TPO) were recorded. EAT was measured with transthoracic echocardiography.

Results
Fat mass, BMI, WC, and WH/Ratio, visceral and abdominal fat mass were higher in the study group than the control group (P<0.05). While there were no differences in terms of FPG (P=0.780), there were significant differences regarding LDL-C and TGs between the two groups (P=0.002 and P=0.026 respectively). Serum TSH and anti-TPO levels were found higher and FT4 level P=0.026 respectively. While positive correlation was found between EAT and demographic parameters and serum TG levels (P<0.05), no correlation was found between EAT and TSH, FT3, fT4, LDL-C, and anti-TPO level (P>0.05).

Conclusion
Despite EAT has been playing an important role in predicting subclinical atherosclerosis in SH, this study could not support this. In our opinion, more studies with more number of patients are needed to claim that.
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**EP948**
Elevated neutrophil/lymphocyte ratio in patients receiving any replacement therapy with euthyroid Hashimoto
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Introduction
Neutrophil lymphocyte ratio (NLO), which is obtained from peripheral blood and used as mathematical rates of lymphocyte numbers, is accepted as available and practical indicator of systemic inflammation existence. We aimed to search NLO between Hashimoto’s thyroids patients who have autoimmune thyroid and also include an aetio-pathogenesis auto-inflammatory process, and healthy control group with this study.

Method
59 patients who have been diagnosed as Hashimoto’s thyroidsitis, euthyroid and receive any treatment, 53 people who have no in point of age, BMI among them, totally 112 people have been incorporated to the study. The average age of patients has been counted as 33.8 ±12.8 years and the average age of control group has been counted as 30.1 ±12.4 years. Statistically significant difference couldn’t be determined (P=0.1).

Results
As a result of this study; patient group NLO has been founded as 4.0 ±0.7 and healthy group NLO has been founded as 2.0 ±0.1. Statistically significant difference has been determined (P=0.01). While statistically significant difference hasn’t been determined between healthy group and patient group in point of white blood cell count (7.9 ±0.3 and 7.4 ±0.2, P=0.1) among neutrophil (5.5 ±0.3 and 5.4 ±1.1, P=0.9), the difference has been determined in point of lymphocyte values (2.04 ±0.1 and 3.1 ±0.5, P=0.05). Positive correlation has been determined between NLO and CRP (r=0.6, P<0.0001), thyroid peroxidase immune body level and (r=0.3, P<0.001), anti-thyroglobulin immune body level and (r=0.3, P=0.006), white blood cell count and (r=0.4, P<0.001) and also between neutrophil level and NLO (r=0.265, P=0.007), neutrophil and lymphocyte count (r=0.776, P<0.001).
**Discussion**

Present symptoms show that NLO values have statistically significant increased in euthyroid Hashimoto’s thyroiditis in comparison with healthy control group and it is seen that it correlated with autoantibody level which is used for the diagnosis of disease. In these results, we think that systemic inflammatory process is important in Hashimoto’s thyroiditis aetiology.

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**EP950**

**Radioiodine treatment of Graves’ disease: dose–response analysis**

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Introduction

Despite more than 60 years’ experience with radioactive iodine ¹³¹I (RAI) treatment of Graves’ disease (GD) about the most appropriate dosing regime is still controversial. The objective of our research was to analyse the outcome of RAI therapy in our cohort of patients.

Methods

Retrospectively, we analysed 603 patients with GD (500 women and 103 men, mean age 51.5±12.7 years) treated with RAI. According to recommended practice in Czech Republic, most patients came with at least 1-year history of the disease, in the first or next relapse. Their antithyroid medication was withdrawn 3–4 days before RAI administration. The treatment was considered successful if patients were euthyroid or hypothyroid on follow-up.

Results

Total efficacy of RAI treatment was 74% in 6 months and 88% in 12 months. We divided our cohort into three subgroups according the adjusted dose (adjusted to thyroid volume and 24-h RAI accumulation): i) in the first group (n = 120) with adjusted dose 0.5–5.0 MBq/g the success rate was 54% in 6 months and 72% in 12 months, ii) in the second group (n = 239) with adjusted dose 5.1–8.4 MBq/g it was 71% and 86%, and iii) in the third group (n = 244) with adjusted dose 8.5–77.2 MBq/g it was 86 and 96% respectively. Median adjusted dose in the second group was 6.8 MBq/g. In the detailed analysis of the third group, any further dose increase over 8.5 MBq/g did not result in higher cure rates. In patients with higher thyroid volume (P < 0.001) and higher disease activity (i.e. higher FT₃, FT₄, TSHR-Ab, and 24-h RAI accumulation as well as suppressed TSH), there was an increased risk of treatment failure. The therapy efficacy was not dependent on sex (P = 0.580) and age (P = 0.578).

Conclusion

With adjusted dose of 8.5 MBq/g, very reasonable efficacy was attained. In patients with smaller gland and lower disease activity it was possible to administer lower adjusted dose, ~6.5–7 MBq/g.

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**EP951**

**Serum H-FABP levels in patients with overt hypothyroidism**

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Aim

Overt hypothyroidism affects mostly women with an increased prevalence in individuals by age. Hypothyroidism is associated with accelerated atherosclerotic cardiovascular diseases, possibly caused by the higher incidence of hyperlipidemia, insulin resistance, hypertension which all are associated to hypothyroidism. Heart-type fatty acid binding protein (H-FABP) is specific for cardiomyocytes and a sensitive marker of myocardial injury. The purpose of this study is examining the effect of hypothyroidism on H-FABP levels and carotid artery intima–media thickness (CIMT) level.

Methods

We measured serum H-FABP levels in 33 patients with overt hypothyroidism and age, gender, and BMI-matched 39 control subjects. All participants underwent high-resolution B-mode ultrasonography in order to measure CIMT.

Results

Serum levels of H-FABP were not found significantly different in the patient group in comparison with the controls (1515.87 ± 2143 pg/ml vs 953 ± 416 pg/ml, P = 0.15 respectively). CIMT was significantly higher in the patient group than in the control group (0.53 ± 0.08 mm vs 0.48 ± 0.05 mm, P < 0.05). However, the HOMA-IR and fasting insulin levels did not differ between the two groups (P > 0.05).

Conclusion

Based on the results of this study, H-FABP seems not a useful marker while detecting preclinical atherosclerosis in patients with overt hypothyroidism but CIMT might be useful to detect early atherosclerosis.

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**EP952**

**Evaluation of geriatric patients with hyperthyroidism treated with radioactive iodine-131**

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Introduction

In this study, we aimed to evaluate radioiodine (RAI) treatment efficacy in geriatric patients with hyperthyroidism.

Design

Patients older than 65 years who received RAI treatment were included via retrospective data analyses. Eighty-two patients with hyperthyroidism (average age: 69.9 years, age range: 64–81 years) who received RAI treatment and then followed up for at least 6 months were included in the study. Patients’ clinical and laboratory results were analysed retrospectively. Euthyroid or hypothyroid status at the end of the year after treatment was deemed to be a response to treatment.

Results

Nineteen patients were men (average age: 68.3 years, age range: 64–75 years), the 63 were women (average age: 71.3 years, age range: 65–81 years). According to thyroid ultrasound or physical examination findings, 13 patients had diffuse thyroid hyperplasia, the other patients had non diffuse hyperplasia (nodular or multinodular). RAI treatment was given to the patients once or twice, or three times if necessary. In first RAI treatment, average 12.7 mCi, in second, average 15.1 mCi, and in third, average 20.7 mCi were given orally. 41 (50%) patients were euthyroid, 19 (23.1%) were hypothyroid, and 22 (26.9%) were thyrotoxic. Success rate of RAI treatment was 73.1%. The highest success rate was obtained in geriatric patients who have diffuse thyroid hyperplasia. Serious side-effects were not observed in our patients.

Conclusion

We observed approximately similar success rates with the reported results in RAI treatment of geriatric patients with hyperthyroidism and also side effects of RAI treatment were low. We believe that RAI treatment should be first choice for treatment of hyperthyroidism in geriatric patients, because it is easy to perform and its side effects are very low.

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EP953
Safety and efficacy of rapid thyroid blockade with Lugol’s iodine in the pre-surgical management of Graves’ hyperthyroidism
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Introduction
A significant number of patients are intolerant of anti-thyroid drugs (ATD) and thyroidecomy remains the only treatment option available to patients who decline radioiodine as definitive therapy. As patients with poorly controlled thyrotoxicosis are at risk of developing thyroid storm, optimal pre-operative control of hyperthyroidism is essential. Rapid thyroid blockade (RTB) with the contrast agents sodium iodide and iopanoic acid were attractive treatment options but these agents are no longer available for routine use.

Aims
To explore the safety and efficacy of rapid thyroid blockade with Lugol’s iodine in the pre-surgical management of Graves’ thyrotoxicosis.

Method
Lugol’s iodine (0.2 ml three times a day) was administered to six patients with Graves’ thyrotoxicosis who were resistant to treatment with the conventional ATD, carbimazole, and propylthiouracil. Treatment was started 10 days prior to planned thyroid surgery. TSH at baseline and subsequent fT₄ and fT₃ were measured at fixed intervals prior to thyroidectomy.

Results
All patients were female; mean (±S.D.) pre-treatment fT₄ and fT₃ levels were 30.1 pmol/l (8.12) and 8.8 pmol/l (5.9) respectively. Mean nadir fT₄ and fT₃ levels after treatment were 16.2 and 4.4 pmol/l respectively. Mean percentage fT₄ reduction was 45.2% and mean percentage fT₃ reduction was 40.4%. fT₄ and fT₃ dropped at an average rate of 7.6 pmol/l per day. Mean absolute reductions of fT₄ and fT₃ levels were 13.9 and 4.4 pmol/l respectively. All patients were biochemically euthyroid preoperatively. The mean time to normalise fT₄ was 3.8 days (±S.D. 1.72). On patient experienced transient adverse effects with Lugol’s iodine.

Conclusion
In this pilot study, Lugol’s iodine was effective in rendering patients biochemically euthyroid prior to planned thyroidectomy. The long-term safety and efficacy of rapid thyroid blockade with Lugol’s iodine needs to be assessed in a larger cohort of patients.

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EP954
Higher titre of TSH receptor antibody was associated with better responsiveness of thyroid hormone to antithyroidal drug in Graves’ disease
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Introduction
Antithyroid drug (ATD) therapy is considered as choice of treatment for Graves’ disease; however, the response of treatment varied between patients. Although several studies reported risk factors for relapse after initial treatment, there were few studies for the responsiveness during early treatment period. Method and design
We reviewed 94 patients with Graves’ disease and used their initial TSH receptor antibody (TSHRAb) titre and consequent free T4 levels during follow up periods. Drug responsiveness was defined as the correlation coefficients between decreasing rates of free T4 levels and exposed dose of ATD. We analysed and compared the coefficients of each patient according to clinical characteristics and TSHRAb titre.

Results
The mean age of subjects was 47.1 ± 15.4 years old and male patients were 26 (28%). The mean titre of initial TSHRAb was 19.1 ± 14.0 IU/L. Although the correlation coefficients did not showed significant association with age group (≤ 40 vs. > 40, r = 0.16, 0.16 vs. 0.22 ± 0.13, respectively in three groups (≤ 10, 10.1–20, 20 <)). We could also observe significant correlation between the consequent TSHRAb titre and the responsiveness.

Conclusion
Our results suggest the possible usage of TSHRAb titre to decide the optimal initial ATD dose and its adjustment in early treatment periods.

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EP955
Shear-wave elastography in diagnostics of primary hyperparathyroidism – new application of the method
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Introduction
Shear wave elastography (SWE) is a reliable, objective and reproducible technique in sonographic assessment of tissue stiffness. It is considered to be an improvement of conventional ultrasonographic examination. It was demonstrated to be useful in the diagnosis of many thyroid disorders, such as thyroid cancer, Hashimoto’s thyroiditis or Graves’ disease. The aim of our study was to check if SWE can be supportive in the diagnosis of primary hyperparathyroidism.

Materials and methods
43 patients referred for surgery due to primary hyperparathyroidism were included. In all cases presence of parathyroid adenoma was confirmed by histopathology. Control group consisted of 322 benign thyroid nodules in 98 patients referred for surgery. Maximal elasticity (E₀) of each lesion was recorded.

Results
Mean E₀ value for parathyroid adenomas was 14.4 kPa with s.d. 17.1 kPa; mean E₀ value was 11.1 kPa. For benign lesions mean E₀ was equal to 57.3 with s.d. = 60.6, median = 36.2 kPa. The difference was statistically significant (P = 0.04, r = -0.32).

Conclusions
Parathyroid adenomas turned out to be significantly and distinctly more elastic than benign thyroid lesions – median values of the stiffness differed over three times. SWE can be a useful supportive method in the diagnosis of such lesions. Presence of very soft localises, localised typically near the rear wall of the thyroid may arouse suspicion of primary hyperparathyroidism and hinting further diagnostic, such as measurement of PTH, calcium and phosphate serum concentrations.

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EP956
The role of antithyroglobulin, antiperoxidase and anti-TSH autoantibodies in amiodarone induced thyrotoxicosis or amiodarone induced hypothyroidism (a two-center study)
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Purpose
In the recent study it has been reported, that elevated serum concentrations of TSH receptor (TSH-R), antithyroglobulin (Tg), antiperoxidase (TPO) auto-antibodies (Abs) may be observed in the subjects treated for amiodarone induced thyrotoxicosis (AIT) type I, decreased in type II of AIT, or changed in amiodarone induced hypothyroidism (AIH). This study was done to analyse the changes of Tg-Abs, TPO-Abs and TSH-R-Abs titer in euthyroid, hyperthyroid (AIT), and hypothyroid (AIH) patients.

Methods
The study consisted of 217 patients diagnosed in the Chair and Department of Endocrinology, Metabolism and Internal Medicine, Poznan, and 63 patients treated in the Department of Nuclear Medicine, in Warsaw, Poland between January 2003 and December 2014. Titer of serum TPO-Abs, Tg-Abs, TSH-R-Abs were analyzed retrospectively, in euthyroid patients with the history of hyperthyroidism prior to re-administration of amiodarone (group A), patients with AIT who discontinued AM therapy (group B), patients with AIT chronically treated with AM (group C), and hypothyroid patients (AIH, group D).

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EP957
Rho/Rho-kinase gene expressions in Graves’ disease and Hashimoto’s thyroiditis

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Introduction
Autoimmune thyroid diseases result from a dysregulation of the immune system leading to an immune attack on the thyroid. Autoimmune thyroid diseases, which include Graves’ disease (GD) and Hashimoto’s thyroiditis (HT), are characterised by lymphocytic infiltration of the thyroid parenchyma. The mechanisms that trigger the autoimmune attack to the thyroid are not entirely known. The aim of this study was to investigate the possible contribution of Rho/Rho-kinase gene expressions in GD and HT.

Methods
A total of 47 patients with GD, 41 patients with HT, and 42 healthy control subjects with similar age and sex were included to this study. mRNA from blood samples was extracted, and real time polymerase chain reaction on the BioMark HD dynamic array system (Fluidigm, South San Francisco, CA) was performed for the Rho/Rho-kinase gene expressions. For calculation of the significance of differences in gene expressions, the Mann-Whitney U-test was used.

Results
Gene expression analysis showed that RHOC, RHOF, RAC1, and ROCK1 mRNA contents in leucocytes were markedly depressed, and ROH1 gene was up-regulated in both GD and HT patients when compared to the control groups (P < 0.05). Although CDC42 gene expression was decreased in GD, it was augmented in HT. Additionally, RHOC, RHOF, RHOD, RHOB, RHOBTB1, RHOBTB3, and RAC3 expressions were significantly suppressed in HT (P < 0.05). There was also decrease in ROCK2 gene expression in HT (P < 0.05). No marked changes were noted in RHOA, RHOB, RHOD, and RND3 (RHOB) genes in GD and HT groups.

Conclusion
In conclusion, to the best of our knowledge, these results are the first to demonstrate the contribution Rho/ROCK gene expressions in GD and HT. Our data showed that these gene expressions may contribute to the pathology of GD and HT.

Disclosure
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EP958
Survey on the steroid dose for patients with subacute thyroiditis in a Korean tertiary hospital

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Introduction
Subacute thyroiditis (SAT) is most common cause of painful thyroiditis. Although prednisolone at 40 mg/d has been preferred as initial dose for moderate to severe SAT, there have also been other recommendations as 25–60 mg/day in many reports. We retrospectively assessed the effect of steroid dose on the SAT.

Methods
We examined 132 patients with SAT who visited our endocrinology clinic at least three times between January 2005 and December 2012. We excluded patients without high ESR level, steroid prescription, and follow-up within 6 months after resolution. Final number of subjects was 63. The outcome in the group with initial steroid dose less than 30 mg (n = 22, 34.9%) was compared with that with 30 mg or more (n = 41, 65.1%).

Results
The mean age of the total patients was 48.2 years. The incidence was most prevalent from September to November (40%, n = 26). The mean of initial prednisolone dose was 30.2 mg, while tapering steroid dosage for the mean duration of 7.6 weeks. Six patients (9.5%) have relapsed within 6 months. The clinical outcome in the group with less dosage was not significantly different from that in the group with more dosage, such as total administration period (P = 0.804), the recurrence rate (P = 0.423), TSH (P = 0.826), free T4 (P = 0.072), ESR (P = 0.079), 99m-TcTetrofosmin thyroid scan uptake (P = 0.186). Although no serious side effect was observed, three cases of epigastric discomfort and swelling was reported in higher dosage group.

Conclusion
In our study, the initial dosage for the treatment of SAT with less than 30mg appeared as effective as 30 mg or more. Relapse of SAT seemed not dependent on the initial dose of prednisolone.

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EP960
Surgical and pathological changes after radiofrequency ablation of thyroid nodules
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Background
Radiofrequency ablation (RFA) is an effective technique for the treatment of symptomatic benign thyroid nodules. It is not known to what extent RFA may affect thyroid surgery and/or histological diagnosis.

Materials and methods
Patients were treated with RFA and then followed for 2 years. RFA was performed on 64 symptomatic Thy2 nodules and on six symptomatic Thy3 nodules, without atypical cells or BRAF or NRAS mutations, in surgically high-risk individuals or patients unwilling to undergo surgery. Volume reduction was evaluated at 1, 3, 6, 12, and 24 months after the procedure. Two Thy3 nodules regrew after the procedure, and the patients accepted to undergo a total thyroidectomy. Here we present how RFA has affected their operation or the final pathology of the surgically removed nodules.

Results and conclusions
RFA is effective for the treatment of Thy2 nodules. RFA should not be used for the treatment of Thy3 nodules, as it only delays surgery in case of malignancy. One session of RFA does not affect subsequent thyroid surgery and/or histological diagnosis.

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EP961
Serum total sialic acid levels in overt and subclinical hypothyroid patients and its relationship with atherosclerotic risk factors
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Objective
Serum total sialic acid (SA) concentration is assessed as an up to date risk indicator of atherosclerosis and cardiovascular diseases.

Methods
It was aimed to investigate about how SA levels are effected in overt or subclinical hypothyroidism (SH) and how it’s associated with other atherosclerosis risk factors because there is no study about these topics, though SA is intensively studied in recent years.

Patients
Sixty newly diagnosed treatment-naive hypothyroid patients (35 subclinical and 25 overt) and 30 euthyroid individuals were included in the study. Fasting blood samples were taken and SA, serum homocystein and hsCRP was measured in addition to routine biochemical measurements and carotid artery intima media thickness (CIMT) measurements were performed.

Results
Diastolic blood pressure, CIMT, Total-C, LDL-C, TG levels were significantly increased in patients. Other atherosclerosis related measurements such as systolic blood pressure, uric acid, hsCRP and homocystein levels were also increased in patients, but not statistically significant. Serum total SA levels were higher in hypothyroid patients compared to controls but the difference was not statistically significant. In patients’ group positive correlation between CIMT and SA was determined as it was between SA and uric acid.

Conclusions
Interesting result of our study is the positive relationship between SA and CIMT which is revealed for the first time. The existence of correlation between SA and some indicators like CIMT, hsCRP and uric acid in hypothyroid group suggests that it can be an atherogenesis indicator in hypothyroid patients.

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EP962
Lifestyle intervention reduces TPO antibody level in euthyroid patients: a retrospective cohort study
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Objective
To investigate the impact of lifestyle intervention on elevated thyroid peroxidase (TPO) antibody levels in outpatients with normal thyroid function.

Methods
A retrospective cohort study was performed to observe and evaluate euthyroid patients with excessive TPO antibodies that presented to the authors’ hospital between March 2013 and October 2014 for routine medical examinations. The subjects were randomly divided into the lifestyle intervention group and the control group. Lifestyle interventions, including diet improvement and adequate sleep, were instituted immediately following the medical examination for 12–24 weeks. Both groups had patients taking either selenium supplements or Chinese herbal medicines. The difference between the two groups in TPO antibody level was compared after lifestyle intervention.

Results
The TPO antibody level decreased by 30% in the intervention group and only 5% in the control group (P<0.05).

Conclusion
Increased TPO antibody level is often related to autoimmune thyroid disorders and inflammation, including conditions such as toxic goitre or autoimmune thyroiditis. The present cohort study demonstrated that lifestyle intervention can effectively improve early-stage thyroid disorders.

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EP963
Beware Carbimazole induced agranulocytosis in amiodarone induced thyrotoxicosis: recovery with Filgrastim
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Agranulocytosis is a rare and serious complication of Carbimazole. (risk <1/106 of population/year. It is associated with higher doses. We report two cases over 1 year in patients exposed to amiodarone.

Case 1: A 63 year old man with ischemic cardiomyopathy had been treated with amiodarone for atrial fibrillation for 3 years. 6 months after stopping he developed symptomatic thyrotoxicosis and started on carbimazole 60 mg per day. Thyroid T4 uptake was low. (Probable type 1 or mixed amiodarone thyrotoxicosis AIT). 3 months later he presented with sepsis and a neutrophil count of 0.010 × 10^9/L and was treated with Filgrastim and antibiotics. Granulocytes rose >1.000 × 10^9/L on day nine of treatment Thyrotoxicosis resolved after 3 months on prednisolone and a short course of potassium perchlorate.

Case 2: A 72 year old female with atrial fibrillation, diabetes and ES renal disease previously on amiodarone for 2 years developed symptomatic thyrotoxicosis and was treated with carbimazole 60 mg per day on a reducing regime. 2 months later she developed agranulocytosis and sepsis: neutrophil count 0.010 × 10^9/L. Probable type 2 AIT induced thyrotoxicosis. She was treated with Filgrastim and antibiotics. Neutrophil count rose to >1.000 × 10^9/L after 6 days. She became euthyroid after prednisone therapy.

Risk for carbimazole induced agranulocytosis may be do the combination of high doses and older age predisposing these patients to agranulocytosis. Because of the cross reactivity of antithyroid drugs treatment of thyrotoxicosis is particularly difficult with the risk of thyroid storm during sepsis. Amiodarone induced thyrotoxicosis can be slow to respond to antithyroid drugs and higher doses are often necessary. Both our patients had accelerated recovery with Filgrastim. We advise caution with high antithyroid drug doses in amiodarone induced thyrotoxicosis and suggest considering combined therapy early.

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Elevated TSH (in upper limit of normal) and insulin resistance
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Introduction
Level of TSH respond to fluctuations in serum free (FT4) but remain in a very narrow individual range. Thyroid function tests are intrinsically linked to variables of insulin resistance and endothelial function. It is possible that underlying factors lead simultaneously to increased serum TSH, insulin resistance, even within current normal TSH levels.

Description of methods and design
We aimed investigate the patients with upper limit TSH and insulin resistance in patients of our out-patients clinics of endocrinology where they were adressed for obesity. Serum insulin, C-peptide and TSH Levels were measured by chemiluminescence method on advice centron XP and HbA1C measured by immune – inhibition on Advia 2400 chemistry system (Siemens Healthcare Diagnostics Inc).

Results and conclusion
Some characteristics of study group (means ± s.d.) (totaly 152 patients): age (years): 49.7±14.8, systolic blood pressure (mm/Hg): 128.8±19.2, diastolic blood pressure (mm/Hg): 78.3±9.6, fasting blood glucose (mg/dl): 110.3±45.2, HDL (mg/dl): 57.4±13.5, insulin (IU/ml): 12.2±11.4, C-peptide (mg/ml): 3.04±1.71, TSH (mIU/ml): 2.56±2.7, FT4 (ng/ml): 1.28±0.47, weight (kg): 84.5±18.7, BMI (kg/m²): 32.2±7.5, circumference of waist (cm): 98.9±16.3, WHR (waist/hip ratio): 0.87±0.07. When we divided into two group according to TSH levels. We found hyperinsulinemia (P<0.04), elevated C-peptide levels (P<0.01), and WHR (P<0.04) in the second group. This findings could justify the increased risk for insulin resistance associated disorders, such as cardiovascular disease, observed in patients with high TSH levels.

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Hypothyroidism and platelet parameters evaluation: a preliminary study
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According to the findings of recent epidemiological research, thyroid complaints are among the most frequent endocrine illnesses in Italy. Being positively correlated to MPV, the mean platelet volume, in subjects with hypothyroidism, it has been hypothesised in literature that TSH can have a probable prothrombotic effect. The mean platelet volume (MPV), PCT (plateletcrit), PDV (platelet distribution width) and P-LCR (platelet large scale ratio) indicate the dimensions of platelet circulating uniformity.

Aim
The study seeks to evaluate whether platelet indicators can undergo alterations in individuals affected by subclinical and clinical hypothyroidism.

Materials and methods
Between September and December 2014, 60 individuals of both sexes between 18 and 45, all unaffected by other pathologies, were enrolled: 20 with hypothyroidism, 20 with subclinical hypothyroidism and 20 controls. These consented to give peripheral venous blood samples for a complete electromicrotometric examination so as to determine platelet indicators, FT4, FT3, TSH thyroid hormones. The PT, APTT coagulative parameters and fibrinogen I levels of the single parameters were statistically evaluated with parametric analyses (t-test of Student) and linear mixed model.

Results and conclusions
Evaluation of the findings yielded that the P-LCT and PCT remained unaltered. Neither were in a state of conlamed hypothyroidism or sub-clinical hypothyroidism (P-value P-LCT=-0.36 and 0.38, P-value PCT 0.75 and 0.90 respectively). However, the MPV and PDW seemed to undergo statistically significant modifications in patients with subclinical hypothyroidism (P-value 0.0000199-0.0159) and in patients with conlamed hypothyroidism (P-value 1.152 and 0.012), thus reflecting a hypothetrical increase of thrombotic risk in such patients. With a view to being able to use the MPV and PDW as useful and affordable cardiovascular illness risk evaluation parameters, it is hoped that research upon more numerous sample populations may be forthcoming.

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molecular mechanisms by which claudins affect tumourigenesis remain largely unknown.

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**EP968**

The effect of thyroid hormone replacement on treatment schedule

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Introduction

Levothyroxine sodium (LT4) is widely used thyroid hormone to treat hypothyroidism. It is generally recommended to take it in the morning and hungry. Several studies about timing of thyroid hormone administration have shown different effects on TSH and FT4. The aim of this study is to determine the effects of timing of LT4 administration on TSH and the clinical outcomes.

Method

The study group includes 65 patients with primary hypothyroidism who take a minimum dose of 50 mg levothyroxine sodium 30 min before the breakfast. Whether their serum TSH is within the laboratory reference range (0.5–5.75 mIU/l) has been examined. We have suggested the patients to take LT4 at bedtime instead in the morning and the patients have been observed for 3 months.

Five patients have been excluded from the study for several reasons. At the end of the study parameters such as TSH, FT4, lipid levels, BMI and clinical outcomes have been evaluated.

Results

Compared to the morning intake, LT4 was taken at bedtime were an increase in free T4 level of 0.06 ± 0.20 (P = 0.025) and an increase in body weight of 0.76 ± 1.53 (P < 0.001). The TSH levels have shown no significant difference between morning and bedtime intake of LT4 (P = 0.05). When the clinical outcomes are evaluated, night sweating in ten patients (% 16.7; P < 0.001) and in eight patients (%13.3; P < 0.001) increase in appetite have been observed.

Conclusions

Our study showed that use of LT4 in the morning and at night had similar effects on serum TSH. However, bedtime intake of LT4 has resulted in increase of sweating, appetite and weight.

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**EP969**

Estimation of iodine intake in pregnant women living in Northern Ireland using a validated food frequency questionnaire

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Adequate iodine intake during pregnancy is required for the production of thyroid hormones and brain development in the foetus. Recent evidence has suggested re-emergence of mild iodine deficiency in the UK possibly due to changing farming practice. A recent multicentre survey in the UK reported that 68% of school girls were iodine deficient with the lowest levels seen in Northern Ireland (NI). Unlike many countries, the UK does not have a salt or food iodination programme. A cross-sectional survey of 264 schoolgirls, aged 14–15 years of age, was carried out in Belfast and Derry/Londonderry as the initial part of an Island of Ireland wide survey (seven centres). These are the two largest cities in NI and both located on the coast. Belfast is more southern with a latitude of 54.583 vs 54.998. Participants were surveyed in spring and winter months to look for seasonal differences. Urinary iodine levels were measured from morning spot urine samples using a standardised Sandell-Kolthoff colorimetry method. World Health Organisation defines deficiency as follows: mild 50–99 μg/l; moderate 20–49 μg/l; severe < 20 μg/l. Median urinary iodine level was 119.1 μg/l (IQR 78.3–166.3). Ninety participants had mild deficiency (34%) while 14 had moderate deficiency (5.3%) and none surveyed had severe deficiency. There was no significant difference in urinary iodine level between spring and winter seasons and no difference between the two cities. Therefore of the schoolgirls surveyed in NI 39% were iodine deficient. These results are in keeping with the previous UK survey and completion of the study in the other five geographical areas will enable a clearer understanding of the extent of this public health issue.

Disclosure

Safefood (project reference 01-2013).

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**EP971**

The role of detecting BRAF T199A mutation in fine-needle aspiration biopsy in pre-operative diagnosis of nodular goitre

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Introduction

Molecular testing play increasingly a significant role in pre-operative diagnosis of nodular goiter, as standard methods may not give conclusive decision in choosing optimal treatment approach. BRAF gene mutations are often discovered in the cytological specimens among the patients with papillary thyroid cancer. The aim of the study was to assess the incidence of BRAF T1799A mutation in cellular specimens derived from fine needle aspiration biopsy (FNAB) of thyroid nodules.

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**EP972**

Pentraxin 3 levels in patients with Hashimoto disease

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Pentraxin 3 (PTX3) is produced from several cell types in case of inflammation. PTX3 has been investigated in several autoimmune diseases. As Hashimoto disease is an autoimmune disease of thyroid, we investigated the role of PTX3 levels in patients with Hashimoto disease.

**Objective**

The aim of this study was to investigate the relationship between PTX3 and autoimmune thyroiditis.

**Methods**

The study subjects were classified as four groups. Group 1: Control group included 42 euthyroid healthy women with negative autoantibody. Group 2 included 27 euthyroid women with positive autoantibody. Group 3 included 46 subclinical hypothyroid women with positive autoantibody (TSH 5–10 mU/L). Group 4 included 39 hypothyroid women with positive autoantibody (TSH > 10 mU/L). PTX3 values were measured with ELISA method.

**Results**

No significant difference was found for PTX3 level between patients with autoimmune thyroiditis and control group. The highest PTX3 level was determined in fourth group. There was a positive relation between PTX3 and TSH level in all groups. There was also a positive correlation between PTX3 and cortisol level.

**Conclusion**

This is the first study investigating the relationship between PTX3 and autoimmune thyroid disease. Although PTX3 levels were positively associated with TSH levels, we couldn’t find any difference in PTX3 levels between our groups.

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**EP973**

Morphological and functional alterations of thyroid gland during treatment with tyrosine kinase inhibitors in advanced renal cell carcinoma

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Background

Sunitinib (SUN) is a novel oral multitarget tyrosine-kinase inhibitor (TKI) that has demonstrated its efficacy in the treatment of metastatic renal cell carcinoma (mRCC). The thyroid dysfunction is one of the most common side effects of SUN. The mechanisms inducing thyroid dysfunction are still poorly understood.

**Aim**

Identify the incidence, severity, ultrasonographic changes and pattern of response of thyroid function tests during treatment with SUN.

**Methods**

This ongoing prospective observational study to date has completed the evaluation of 25 mRCC patients: ten women (59±18 years) and 15 men (65.5±7 years). 5/25 patients received LT4 replacement therapy and 11/25 had thyroid nodules at enrollment. SUN was administered at daily dose of 50 mg (schedule 4/2). Thyroid function tests were assessed at baseline and at week-4 and -6 of each cycle, ultrasound at baseline and after the first and the third SUN cycle.

**Results**

We observed an increase in TSH values, most frequently after the second cycle of SUN (mean-TSH 17.05±4.36 mU/l) and in older men (mean-TSH 91.95±106.4 mU/l). TSH rose above normal range (0.35–4.94 mU/l) only in patients which were not on LT4 replacement at enrollment. Half of untreated patients had an TSH elevation requiring LT4 replacement after the first cycle; all of them required a further dosage increase after the second cycle. No dose-adjustment was needed in patients already on LT4 at enrollment. In all patients, a volumetric reduction of thyroid lobes occurred at week-6. Ultrasound at week-18, detected the appearance of a hypoechoic solid nodule in one patient and a volumetric increase of pre-existing nodules in two other patients.

**Conclusion**

SUN is associated with thyroid functional and morphological changes occurring rapidly, within few weeks, in most but not all patients. Distinct individual patterns of response to TKI are identified allowing a better prognosis and management.

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**EP974**

Thyroid autoimmunity may effect on mean platelet volume

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**Aim**

Mean platelet volume (MPV) is considered a new indicator of atherosclerosis. Activated platelets and subclinical inflammation predispose to create for atherosclerotic heart disease. Larger platelets are metabolically more active than smaller ones and have more protrombotic potential. We have recently demonstrated that MPV levels in Hashimoto’s patients tend to be higher than healthy controls even if in euthyroid state. In present study we aimed to investigate a relationship between MPV and autoimmune thyroid disease.

**Materials and method**

Patients with Hashimoto thyroiditis (HASH) (58 euthyroid Hashimoto thyroiditis (EHASH) (mean age 43.4±12.4 year)) and 42 hypothyroid (HPHASH) (mean age 46.7±15.5 year)) and 81 patients with Graves disease (GD) (mean age 38.8±13.5 year) who referred our endocrinology outpatient clinic due to high thyroid autoantibodies as antithyroid peroxidase (Anti-TPO) and/or antimyoglobulin (Anti-Tg) and/or TSH receptor antibody were included in the study. 57 (age-matched 46.4±11.6 year) euthyroid control subjects were taken into the study. All study population were evaluated by hormonal and platelet parameters.

**Results**

Serum Anti-TPO levels in all study groups (EHASH, HPHASH, GD) were significantly higher than those control subjects (P=0.001, P=0.0001, P=0.0001 respectively). The MPV in patients with EHASH, HPHASH, GD were also found significantly higher than control group (P=0.046, P=0.044, P=0.002 respectively). No statistically significant differences were found between the other parameters such as the platelet count, platelet distribution width and plateletcrit. We found that MPV increased independently of presence of age, sex and TSH in chronic autoimmune thyroid diseases (β=0.074, P=0.007). There was a significant correlation between MPV and anti-TPO levels (r=0.145, P=0.027).

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Discussion
Our findings suggest that change of autoimmune in thyroid gland in patients with chronic autoimmune disease may be effect on MPV level as well as tend to create cardiovascular risk because of large platelets have more metabolically active.

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EP975

Body composition after treatment of subclinical hyperthyroidism
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Background
Subclinical hyperthyroidism (SHT) is associated with harmful effects on cardiovascular system, bone metabolism and progression to clinical hyperthyroidism. Loss of weight is a common fact in patients with clinical hyperthyroidism. Subclinical hyperthyroidism (SHT) is associated with harmful effects on cardiovascular system, bone metabolism and progression to clinical hyperthyroidism. Loss of weight is a common fact in patients with clinical hyperthyroidism.

Objectives
To assess changes in body composition after radioiodine therapy for SHT due to toxic nodular goitre.

Methods
Prospective controlled cohort study. Patients with persistent SHT due to toxic nodular goitre received a single fixed dose of 131I (555 MBq). A control group was established with patients who preferred to delay treatment. Body composition (lean mass, fat mass and bone mineral content) was determined by dual-energy X-ray absorptiometry (DEXA) at baseline and 12 months after.

Results
Twenty-nine patients were studied (age 69.5 ± 11.5, 75.9% women; BMI 27.1 ± 5.7 kg/m²; serum thyrotropin (TSH) 0.20 ± 0.21 μIU/mL; serum free triiodothyronine (T3) 1.01 ± 0.19 ng/dL, 17 belonging to the treatment group and 12 to the control group. Study groups were comparable. No longitudinal changes in body composition were noted in either group, except for a trend to gain fat mass. In both groups, no difference in basal TSH levels was shown between patients assigned to different treatments (group A: TSHtab = 10.1 ± 1.8, TSHsol = 9.6 ± 2.2; group B: TSHtab = 7.1 ± 1.2, TSHsol = 6.9 ± 2.1; group C: TSHtab = 7.9 ± 1.7, TSHsol = 8.1 ± 2.1). At Tc, TSH values on group A (before eradication of HP) significantly decreased on patients treated with SOL, while on group B and C, equally decreased without difference within two formulations (group A: TSHtab = 7.8 ± 2.6 vs TSHsol = 7.3 ± 1.8, P = 0.001; group B: TSHtab = 2.4 ± 1, TSHsol = 2.6 ± 1.2; group C: TSHtab = 1.7 ± 1.4, TSHsol = 2.5 ± 1.6). At Tc, TSH levels on group A (after eradication of HP) were in the normal range with no significant changes within two formulations; on group B and C, TSH levels were normal without significant difference within two formulations (group A: TSHtab = 2.5 ± 2.6 vs TSHsol = 3.6 ± 1.8, P = 0.03; group B: TSHtab = 3.5 ± 2.2 vs TSHsol = 2.1 ± 1.8, P = 0.093; group C: TSHtab = 1.9 ± 2.1, TSHsol = 2.0 ± 1.7). In each groups, no differences were shown on FT4 values within two formulations. In conclusion this preliminary report suggests that LT4 TAB or SOL are equally efficient to treat SH in dyspeptic patients without gastric alterations or with simple gastritis or CAG, while LT4 SOL seems to be more efficient than TAB in patients with HP infection, independent of its eradication.

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EP977

Clinical case of amyloid goitre due to idiopathic AA-amyloidosis
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Introduction
Amyloid goitre is a rare cause of thyroid enlargement, especially as a reason of fast growth. Here we present unusual case of idiopathic AA-amyloidosis as a cause of rapidly growing goitre.

Clinical case: Patient 36-year-old presented with complaints of shortness of breath and deglutitive problems during 2 months. His medical history was notable for nephrotic syndrome due to AA-amyloid nephropathy and chronic hepatitis C that were diagnosed 8 years ago. At that time in order to determine the cause of AA amyloidosis, there were performed extensive laboratory evaluation, the results of which turned out barren of definitive diagnosis. The pathogenic and symptomatic treatment of nephrotic syndrome was prescribed. 3 years later he was diagnosed with terminal stage of chronic kidney disease, and chronic haemodialysis was started. Physical examination revealed considerably enlarged thyroid gland, and ultrasound was performed. The volume of gland was 163 ml, and there were detected three lesions about 2.5 cm in diameter. The results of thyroid ultrasound, which was performed because of screening for hyperparathyroidism 6 months ago, were normal. In order to determine the nature of lesions there was done fine-needle biopsy, the results of which were consistent with macro-microfollicular goiter. The thyroid function was normal (TSH 0.93 μIU/ml). Since there were objective signs of upper airway obstructive symptoms, there were performed thyroidectomy. Microscopically, the stroma contained deposits of amorphous material characteristic of amyloid. These deposits stained with Congo red and were apple green in colour when examined microscopically under polarised light. Immunohistochemical staining patterns were consistent with AA amyloid. There was extensive fat cell metaplasia in the thyroid interstitium.

Conclusion
The differential diagnosis of rapid thyroid enlargement should include amyloid goitre nevertheless the type of enlargement (in our case it was not typical diffuse manner) and amyloidosis duration if it is present.

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EP978
Pseudothrombocytopenia improved with antithyroid treatment in Graves’ disease: a case report
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Thrombocytopenia can be seen rarely in Graves disease (GD). In this report we present a case of pseudothrombocytopenia in a 21-year-old woman who had hyperthyroidism due to GD. A 21-year-old female admitted to our clinic with symptoms such as hair loss, anxiety, nervousness and tremor in hands. Considering her symptoms, thyroid function tests were evaluated to screen for presence of hyperthyroidism. Her TSH level was low while free T3 and free T4 levels were elevated. There was no nodules seen in her thyroid ultrasonography. An increased radioiodine uptake was found in thyroid gland. Her thyroid receptor antibody (TRAB) was positive. In the light of all these results, GD was diagnosed. Before antithyroid treatment, a complete blood count and liver function tests were ordered. All the tests were normal except low platelet count. She had no bleeding history. Test was reordered using a citrate-containing tube and platelets were found low again. Aggregated platelets were seen in peripheral smear showing that decreased platelet level was due to pseudothrombocytopenia. There was no history of herbal drugs, medicine or any other cause of pseudothrombocytopenia. Methimazole treatment was started. One month after therapy, thyroid function tests came back to normal levels, and TRAB turned to be negative. Interestingly platelet count were turned to be normal in blood tests using both EDTA-containing and citrate-containing tube. Repeated peripheral smear did not contain any aggregation of platelets. Pseudothrombocytopenia was described in only a few case reports in the active phase of some autoimmune diseases like systemic lupus eritematosus. Our case is the first report of pseudothrombocytopenia in GD. We think that normalisation of platelet count after successful antithyroid treatment is important in the evaluation of these patients.

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EP979
Ogilvie’s syndrome and myxoedema crisis: a case report
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Introduction
Ogilvie’s syndrome (acute colonic pseudo-obstruction) is a syndrome in which the clinical features resemble those of mechanical obstruction with massive colonic dilatation, in the absence of any demonstrable evidence of such an obstruction in the intestine. The exact pathophysiology of intestinal pseudo-obstruction remains to be elucidated. Current theories continue to suggest the idea of an imbalance in the autonomic nervous system. The initial therapy remains conservative with supportive measures (Nil Per Os, nasogastric decompression, correction of fluid, electrolyte and metabolic disorders, reduction or discontinuance of drugs that inhibit gastrointestinal motility, and treatment of infections), followed by neostigmine, decompressive colonoscopy and finally surgery if signs of ischemia, abdominal sepsis, or perforation are present.

Case presentation
A 51-year-old Caucasian female patient with a past medical history of hypothyroidism with poor adherence to therapy presented with symptoms of abdominal colic pain, distension and obstipation, associated with nausea, puffiness of the eyes, and adynamia. At observation the abdomen was distended, with normal bowel sounds, diffusely painful to palpation but without signs of peritoneal involvement. There was no altered mental status. Laboratory tests revealed increased creatinine and creatine kinase levels, normocytic normochromic anaemia, hypokalaemia, and normal glycaemic levels. Thyroid profile and ultrasonography were suggestive of primary hypothyroidism. Tomography images were consistent with Ogilvie’s syndrome with proximal colonic dilatation until a cut off at the sigmoid, without any structural lesion visualised. The colonoscopy performed was normal. The patient underwent hormone replacement therapy, as well as supportive measures, evolving with progressive clinical and radiological improvement after a few days.

Conclusion
This case illustrates a rare association between myxoedema crisis and Ogilvie’s syndrome and the importance of prompt recognition and treatment of reversible medical causes, after excluding mechanical large bowel obstruction.

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EP980
Effect of l-thyroxine on left ventricular function in subclinical hypothyroidism
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Introduction
Thyroid hormone deficiency can lead to the impairment of cardiac function. Whether subclinical hypothyroidism (Sch) is a risk factor for left ventricular (LV) dysfunction is controversial. Aim of the study was to assess whether Sch is associated with LV systolic and diastolic dysfunction and its reversibility after treatment with l-thyroxine.

Material and methods
Twenty-seven consecutive patients with newly diagnosed Sch underwent laboratory analyses (TSH, FT4, T3, anti-TPO, and anti-Tg antibodies), and a complete two-dimensional echocardiography study.

Results
Analysed patients have the following characteristics: age 41 ± 12 years, TSH 8.5 ± 2.7 mU/l before treatment, and TSH 2.07 ± 0.9 mU/l after an average follow-up period of 7.2 ± 1.9 months. Compared to baseline measurements, after 5 months euthyroid stage the duration of the A wave was shorter (112.18 ± 17.2 ms vs 112.18 ± 17.2 ms, P < 0.01), and the longitudinal global strain was higher (−20.07 ± 2.7 % vs −19.55 ± 2.3 %, P < 0.05). Free T4 positively correlated with E/A ratio (r = 0.42, P < 0.05) and T3 negatively correlated with DT (r = −0.50, P < 0.05). Univariate regression analysis showed a statistically significant independent effect of TSH on the E/e’ ratio, E/e’ average, LVED vol, LA, and LA area.

Conclusion
Subclinical hypothyroidism is associated with systolic and diastolic LV dysfunction, as well as reducing global longitudinal LV systolic function. These alterations may be reversed by l-thyroxine.

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EP981
Is there any effect of the treatment on mean platelet volume in patients with hypothyroidism and hyperthyroidism?
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Introduction
Mean platelet volume (MPV) which is part of a complete blood count measures the platelet size. There are many studies in the literature that it is an indicator of platelet function in thrombotic and inflammatory diseases. However, the number of studies about changes in MPV after treatment in thyroid disease is very limited. In this study, we aimed to reveal the MPV change with treatment in patients with hypothyroidism and hyperthyroidism.

Materials and methods
After approval from the ethics committee (400 patients (mean age: 51.24 ± 13.62) were retrospectively examined. Two groups were created as 200 patients (21 males and 179 females) with hypothyroidism and 200 patients (26 males and 174 females) with hyperthyroidism. Regularly followed up patients having no other
inflammatory acute and chronic disease and without malignancy were included in the study. Before and after treatment in the outpatient follow MPV and TSH values were compared.

Results
TSH level is found 9.54 and 2.18 μIU/ml pre-treatment and post-treatment period respectively ($P < 0.001$) in hypothyroid patients. Pre-treatment TSH level is 0.09 μIU/ml and also post-treatment level is 0.62 μIU/ml ($P < 0.001$) in hyperthyroidism group. There is significant difference between MPV values before and after treatment in hypothyroidism and hyperthyroidism group and also MPV values increased in both groups after treatment ($P = 0.001$).

Conclusion
It is known that MPV decreases in inflammatory events and MPV increases with regression of inflammation. Those results of hypothyroidism which is in group of autoimmune thyroid diseases can be interpreted in terms of the presence of inflammation. The reason for the changes in MPV in our study can be explained in terms of the effect of the treatment of inflammatory.

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EP982
Co-occurrence of Graves’ disease and immune thrombocytopenia: a case report
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Also cytopenias can be established in the evaluation of Graves’ disease (GD), isolated thrombocytopenia is very rare. Here, we present a case of immune thrombocytopenia incidentally found in the evaluation of GD. A 48-year-old female was admitted to our hospital with palpitation and anxiousness. The thyroid function tests were concordant with thyrotoxicosis. She had two subcentimetre nodules in the right thyroid lobe. Thyroid gland had increased iodine uptake. And thyroid scan showed a diffuse hyperactive thyroid gland. GD was diagnosed. She had isolated thrombocytopenia in her complete blood count (37 000/μl). She had no history of bleeding, chronic illness, medication, or herbal drugs. Peripheral smear was concordant with platelet count. Her haemoglobin level was normal. Antinuclear antibody was negative. Immune thrombocytopenia was diagnosed. As she had platelet levels above 20 000/ml we decided to initially start methimazole therapy without steroid therapy. In the first month of methimazole therapy, platelet counts were defined between 25 000 and 45 000/μl. But 6 weeks after methimazole therapy, when her free $T_4$ and free $T_3$ levels were in the normal range, her platelet count began to decrease. Prednisolone treatment was initiated for immune thrombocytopenia. Platelet count rapidly increased to normal levels. Steroid therapy gradually tapered and stopped after two months. Four months after discontinuing steroid treatment, she is now euthyroid with methimazole therapy, and her platelet count is fluctuating between 100 000 and 120 000/μl.

Discussion
There were only a few case reports describing co-occurrence of GD and immune thrombocytopenia. A hypothesis of cross reaction between antithyroid antibodies and platelet epitopes were discussed. Although some literature supported this hypothesis, there were only a few case reports describing co-occurrence of GD and immune thrombocytopenia: a case report

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EP983
Insulin resistance and low folate levels are associated with hyperthyroidism in Graves’ disease
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Objective
To evaluate the interrelationships between thyroid function, insulin resistance, lipid profile, homocysteine, C-reactive protein (CRP), folic acid, and vitamin B12 levels, in Graves’ disease (GD).

Methods
We recorded thyroid function tests, BMI, insulin resistance markers, lipid profile, homocysteine, CRP, folic acid, and vitamin B12 levels, in 104 subjects with GD in the first cycle of treatment with methimazole. 94% of whom were female. The subjects were classified into two groups: 49 patients were included in the hyperthyroid group ($T_4 > 3.71$ μg/ml and/or $T_3 > 1.48$ ng/dl, and TSH <0.35 Ul/ml) and 55 in the euthyroid group. Statistical analysis was performed with Mann-Whitney U test, logistic regression, and Pearson’s correlations test.

Results
Results are expressed as median and percentiles (25–75). A two-tailed $P$ value <0.05 was considered significant.

Results
Significantly higher levels of TRAb (Ul/ml) were found in the hyperthyroid patients (3.2 (1.5–12.1) vs 3.1 (0.5–3.0), $P = 0.001$). The levels of folate (ng/ml) and WBISI were significantly lower in the hyperthyroid group (5.1 (3.6–6.5) vs 6.9 (5.1–9.4), $P = 0.001$ and 4.39 (2.49–6.15) vs 5.50 (4.08–7.79), $P = 0.015$). Across all patients, TSH levels were positively correlated with folate ($r = 0.240$, $P = 0.021$), HISI ($r = 0.217$, $P = 0.046$), and WBISI ($r = 0.356$, $P = 0.001$) and negatively correlated with TRab ($r = -0.461$, $P < 0.001$), HOMA-IR ($r = -0.218$, $P = 0.045$), and IGI ($r = -0.313$, $P = 0.004$). The levels of $T_3$ and $T_4$ were positively correlated with HOMA-IR ($r = 0.284$, $P = 0.028$ and $r = 0.325$ and $P = 0.016$) and negatively correlated with HISI ($r = -0.283$, $P = 0.009$ and $r = -0.261$, $P = 0.016$) and WBISI ($r = -0.233$, $P = 0.032$ and $r = -0.260$, $P = 0.016$). Negative correlations were also found between $T_3$ levels and QUICKI ($r = -0.281$, $P = 0.009$) and between $T_4$ levels and HDL-C ($r = -0.198$, $P = 0.046$). In the hyperthyroid group we found significant correlations between $T_3$ and Lp(a) ($r = 0.367$, $P < 0.05$). In the euthyroid group we found negative correlations between $T_3$ and vitamin B12 ($r = -0.358$, $P < 0.01$)

Conclusion
We found that patients with higher levels of TRab and insulin resistance had a higher risk of being hyperthyroid in Graves’ disease. On the other hand, patients with higher folate levels had a lower risk of being hypothyroid.

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EP984
Urinary iodine concentrations in pregnant women with gestational and pregestational diabetes mellitus
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Introduction
Urinary iodine concentration (UIC) can reflex recent changes in iodine status and serve as a sensitive marker of current iodine intake. The cut-off value of UIC was determined as the level lower than 100 μg/l. Adequate median urinary iodine for iodine intake in pregnancy is 150–249 μg/l. The aim of this study was to map the situation of iodine intake in pregnant women with pregestational and gestational diabetes and to explore relationship with thyroid function.

Methods
We have measured UIC in 252 pregnant women screened positive for pregestational or gestational diabetes in second trimester of pregnancy. Currently, serum levels of autoantibodies against thyroid peroxidase (TPOAb) and thyroglobulin (TgAb), TSH, and free thyroxine (fT4) were determined.

Results
Median UIC was 90.90 μg/l (range 20–4725 μg/l). In 222/252 (88.1%) women UIC was lower than 150 μg/l (median 85.70 μg/l) and in 151/252 (59.9%) was lower than 100 μg/l. UIC in the range appropriate with mild iodine deficiency (50–149 μg/l) was measured in 195/252 (76.2%) women and 27 (10.7%) values were found in the range of moderate deficiency (20–49 μg/l). Any value of UIC was lower than 20 μg/l. In nine women were measured levels in the adequate range of 150–249 μg/l. In 222/252 (88.1%) was UIC higher than 249 μg/l (median 305.1 μg/l). In women with the UIC <150 μg/l was found significantly higher serum TSH in comparison to them with UIC ≥ 150 μg/l (1.866 mIU/l vs 2.079 mIU/l, $P = 0.001$).

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Conclusion
In total 88.1% of women screened positive for gestational or pregestational diabetes were iodine deficient in second trimester of pregnancy and had slight elevation of serum TSH as compared to them with sufficient iodine intake.

Disclosure
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EP985
Beware false positive lymph node biopsies in patients with chronic lymphocytic thyroiditis
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A 40-year-old lady who was 4 months postpartum, presented with clinical and biochemical features consistent with post partum thyroiditis associated with neck swelling. She had a family history of autoimmune thyroid disease. She underwent ultrasound guided fine-needle aspiration (FNA) biopsy which was reported as Thy1f and listed for diagnostic hemithyroidectomy. She presented to us for a second opinion. She was on replacement therapy and the anterior neck swelling has resolved. Thyroid antibodies were negative. Thyroid ultrasound was repeated showing a diffusely lobular thyroid consistent with background thyroiditis with associated lymphadenopathy. The isthmus ‘thyroid node’ that was previously biopsied was noted to be extrathyroidal isthmus lymph nodes in close proximity to the thyroid. Patient was discussed in a multidisciplinary meeting (MDT) with confirmation that the original cytology was reflective of lymphocytic thyroiditis. She was advised that surgery was not indicated but she will be actively monitored clinically.

Sonographic features of chronic lymphocytic thyroiditis (CLT) include the following: hypoechogenic and heterogeneous, pseudomacronodular (‘swiss cheese’ or ‘honeycomb’ pattern), pseudomacronodular, profoundly hypoechogenic, developing fibrosis, hyperechoic, and speckled. Pseudomacronodular appearances may be confused with a multi-nodular goitre. With the pseudomacronodular pattern the area of inflammation is larger. The skilled sonographer need to be able to appreciate both these patterns as they may be misinterpreted for thyroid nodules. Reactive lymph nodes are almost universally found in CLT; they are commonly found in the pretracheal and paratracheal region as well as at levels III and IV. Given the higher prevalence of papillary thyroid cancer in CLT, such lymph nodes need to be distinguished from malignant lymph nodes using the same sonographic criteria as per patients without CLT. Isthmus lymph nodes can be mistaken for thyroid nodules given their close proximity to the thyroid potentially leading to unnecessary investigations and treatment.

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EP986
Propylthiouracil induced anti-neutrophil cytoplasmic antibody-associated vasculitis with skin lesions and granulocytopenia
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Propylthiouracil (PTU) is a widely used drug, and can cause drug-induced vasculitis which is characterized by inflammation and cellular infiltration of small vessels and presence of anti-neutrophil cytoplasmic antibodies (ANCA). We report a case of perinuclear antineutrophil cytoplasmic antibody-associated vasculitis developed during treatment with PTU for Graves’ disease. A 58-year-old woman admitted to the Emergency Department with painful necrotic lesion at her right ear and left arm for 15 days. Ear lesions were considered as ectyma gangrenosum in an ENT clinic 10 days ago and anti-pseudomonal treatment had begun but no amelioration observed. Her medical history was significant for type 2 diabetes for 12 years and Graves’ disease for 4 years. There had been a similar lesion at her left ear 6 months ago resulted with auto-amputation. She had been using PTU 100 mg/day and pre-mixed insulin injection twice a day. We found non-tender, mobile cervical lymphadenopathies, enlarged liver and spleen together with ear lesions in physical examination. Her laboratory tests revealed normal thyroid function, leukopenia, neutropenia and normochrom normocytic anaemia, high CRP and sedimentation with p-ANCA and anti-MPO positivity. Biopsy of the affected skin revealed leukocytoclastic vasculitis. As additional tests excluded systemic vasculitis, propylthiouracil-induced vasculitis was diagnosed. Propylthiouracil was discontinued and the skin lesions disappeared, granulocytopenia has revealed over time without the need of any specific therapy.

Conclusion
Physicians and also the patients should be aware of the major adverse reactions of anti-thyroid drugs.

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EP987
Haemorrhagic thyroid cyst after breathing exercise
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A 40-year-old gentleman was referred with sudden onset discomfort in the neck associated with the development of a lump. Earlier that morning he had carried out breathing exercise known as surya krishna at 0600 h and noticed the lump 3 h later whilst shaving. Thyroid USS showed a right-sided thyroid cyst, aspiration of which yielded haemorrhagic contents. FNA of the solid component of the wall did not reveal any malignant cells. The fluid re-accumulated with pressure symptoms including a gritty discomfort when talking, pain and heaviness in this region. Repeat scan did not reveal any significant changes in the appearance of the thyroid cyst. Surya krishna is a breathing exercise lasting 30–60 min with times of hyperventilation and other times of slow breathing. He recalled experiencing pins and needles, numbness and tingling with the hyperventilation but felt energetic at the end of the session. However, at the beginning of the session there is an emphasis placed on breathing through the throat and he remembered exerting a certain pressure in the throat region when doing this. We hypothesise that the pressures involved during the breathing exercises may have been sufficient to cause haemorrhaging within a thyroid nodule. The authors have seen two other cases presenting in a similar manner.

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EP988
Levothyroxine therapy in comparison: fixed vs alternating dosage in subclinical hypothyroidism
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Introduction
Oral levothyroxine (L-T4) is the standard treatment for hypothyroidism and serum TSH represents the best marker for assessing the proper L-T4 dose. The absorption and bioequivalence of different commercial L-T4 preparations might be variable. The aim of this study is to compare the efficacy of L-T4 using alternating doses vs fixed ones.

Methods
Fifty-eight patients with primary hypothyroidism receiving L-T4 therapy. The inclusion criteria were as follows: i) age range between 23 and 75 years and ii) patients with subclinical hypothyroidism (TSH level between 2.5 and 4.5 mU/L), treated with L-T4 oral solution at alternating dosages on consecutively days (75 μg/100 μg, group O) or soft capsules (88 μg/day daily, group T), for at least 6 months. The exclusion criteria were as follows: i) pregnancy or lactation; ii) patients with chronic diseases, such as cardiac (coronary disease or arrhythmias), pulmonary, gastrointestinal (malabsorption disorders), and renal disorders or malignancy; and iii) medications that could interfere with L-T4 absorption.

Results
According to ANOVA for repeated measured with treatment (T vs O group) as between-subjects factor and time (baseline, 45, 90, and 180 days) as within-subjects factor, a significant interaction treatment*time was found (F=3.673, Greenhouse-Geisser df = 1.9, 184.6, P<0.028), indicating two different trends of...
TSH in T and O groups. Contrast analysis (each time vs baseline) showed a stronger TSH decrease after soft capsules at 180 days (O group 2.17±0.55 and T group 1.67±0.59).

Discussion
Our preliminary observation seems to show a possible greater efficacy of l-T4 at fixed dosage vs alternating and consecutive dosage, as suggested by significant greater decrease of TSH levels in group T. This finding could be related to an improving of adherence to l-T4 therapy at fixed dosage. Treatment at alternating dosage on consecutive days may not always be accurate. However, prolongation of follow-up is needed to confirm our data.

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EP989
The relationship between vitamin D deficiency and thyroid autoimmunity in Graves’ disease
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Context
Graves’ disease (GD) is the most common cause of hyperthyroidism. It occurs more commonly amongst women, smokers and patients with other autoimmune diseases or a family history of thyroid autoimmunity. Peak incidence occurs between 40 and 60 years of age but any age group may be affected. Vitamin D deficiency has been reported to link with a variety of autoimmune diseases. However, the relationship between the thyroid autoimmunity in GD and vitamin D deficiency is unclear.

Objective
We aimed to investigate the association of vitamin D and TSH receptor antibody levels (TRab) with GD.

Design and setting
This was a cross-sectional study conducted in education and research hospital. A total of 67 patients with GD (30 men and 37 women) along with 53 age-matched non-GD controls participated in the study.

Main outcome measures
TSH, free triiodothyronine (FT3), free thyroxine (FT4), thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TGAAb), thyrotrophin receptor antibody (TRAb), parathyroid hormone (PTH), calcium, and 25-hydroxyvitamin D (25(OH)D) levels were measured.

Results
25(OH)D levels were significantly lower in the GD group, compared with non-GD control group (P<0.001). 25(OH)D levels was inversely correlated with TRab levels (r = −0.38, P<0.001). However, our results did not show a correlation between the levels of 25(OH)D and the levels TPOAb, TGAAb, FT3, FT4, and TSH. The levels of PTH in serum were increased in TRAb positive GD patients compared to control subjects (P<0.01). Logistic regression analysis results indicated that 25(OH)D levels were not a significant risk factor for developing GD.

Conclusion
In patients with GD, low vitamin D status might be cause of increased titres of TRab, suggesting a possible link between vitamin D status and increased thyroid autoimmunity in GD.

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EP990
Thyroid hormone resistance: a case report
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Classic thyroid hormone resistance (THR) occurs per every 400,000 live birth. THR should be considered along with TSH-producing adenomas when normal or high levels of TSH not consistent with hyperthyroidism is present. A 45-year-old female patient who was operated three times for multinodular goitre had been treated with l-thyroxine. Mammillary biopsy had performed after detection of mass localized in right breast by mammography performed during regular follow-up, then right radical mastectomy was performed due to the diagnosis of ductal carcinoma. In thyroid USG examination, it was found that there were three to four nodules in right thyroid lobe sized 9 × 6.5 mm and nodules with hypoechoic solid-nature which largest of them was 16 × 11 mm in left thyroid lobe. In addition, there were also ovoid-shaped lymph nodes with fatty hiluses in both cervical lymphoid chains as two of them (largest one sized 26 × 5 mm) in right zone 3 and three of them (largest one sized 25 × 6 mm) in left zone 3. Thin needle aspiration biopsy was performed on thyroid nodules and cervical lymph nodes. Results were benign. Cella magnetic resonance imaging (MRI) was performed with diagnosis of secondary hyperthyroidism after detection of elevated TSH, FT3, and FT4 levels in thyroid tests. In cella MRL, it was found that there was an adenoma sized 11 × 9 × 10 mm in hypophysis gland. Other anterior hypophysis hormones were normal. There were no eyesight pathology. l-thyroxine treatment was ceased due to the euthyroid status of the patient. During tests performed for excluding THR, it was found that alfa subunit (ASU) level was in normal range (0.35) and molar ASU/TSH ratio was below 1. These results were consistent with THR. Then, TRH stimulation test was planned. TSH levels at 0, 15, 30, 45, and 60 min after TRH administration were obtained. It was observed that there was an extensive response consistent with THR in TSH levels with TRH test (TSH at 0 min: 8 mIU/mL, TSH at 15 min: 57 mIU/mL, TSH at 30 min: 76 mIU/mL, TSH at 45 min: 75 mIU/mL, and TSH at 60 min: 67 mIU/mL). Hypothyroidism symptoms were not observed in follow-up without medication. Adenoma size had not been changed in control cella MRL. Anterior hypophysis hormones were in normal range. Patient was enrolled in follow-up with the diagnosis of THR and non-functional hypophysis adenoma. In clinical practice, differentiation between THR-secretting adenomas and THR is quite difficult. Predominance of hyperthyroidism symptoms and presence of macroadenoma in hypophysis make the possibility of THR-secretting adenoma more convincing. However, most of the patients are asymptomatic. Considerable elevations in TSH levels increase the possibility of THR-secretting adenoma although thyroid function tests are mostly same in both of these pathologies. TRH stimulation test is the most valuable test for diagnosing. Its sensitivity and specificity were reported as 90% and 80–90% respectively. In conclusion, THR should be considered before diagnosing as THR-secretting adenoma in patients evaluated for secondary hyperthyroidism and identified with hypophysis adenoma.

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EP991
Relationship of thyroid function and central obesity
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The objective of the study was to investigate association between BMI, waist circumference, and measures of thyroid function among euthyroid adult women. Material and methods: We analysed retrospective data of 119 euthyroid women participating in Lithuanian screening and prevention program for patients with high cardiovascular risk at Vilnius Antakalnio Outpatient Clinic from Jul 2013 to Dec 2013. Glucose, lipid profile, TSH, and FT4 tests and ultrasound of thyroid gland records were investigated and thyroid gland volume was calculated using formula: thyroid volume = height × width × depth × correction factor (as 0.524). Results: Mean patients age was 57.04±4.36, BMI 28.80±5.33 kg/m2, waist circumference 88.40±12.24 cm, TSH 1.81±0.92 mIU/L, FT4 12.54±2.89 pmol/l, and mean thyroid gland volume 14 645.46±6453.74 mm3. 36.1% of women were obese and 41.2% overweight. Mean TSH and thyroid gland volume did not differ between groups of obese, overweight and normal weight women. TSH inversely correlated with thyroid gland volume (r = −0.245, P = 0.044, FT4 (r = −0.471, P = 0.042), and positively correlated with waist circumference (r = 0.210, P = 0.036) and BMI (r = 0.184, P = 0.045). After adjusting for age, presents of diabetes and dyslipidaemia significant positive association was observed between TSH and waist circumference (B = 0.17, P = 0.029).
Conclusions

We found that measures of overall and central adiposity were associated with higher circulating levels of TSH in euthyroid women. Although, weight loss and weight gain are well-known consequences of overt thyroid dysfunction, our results suggest that, within the euthyroid range, excess body weight and especially central obesity may induce changes in thyroid hormone levels.

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EP992

Ultrasonographic and cytopathological characteristics of thyroid nodules in Graves’ disease

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Introduction

The risk of malignancy has often been reported to be more frequent in Graves’ disease (GD) than non-autoimmune thyroid nodules. However, frequency of thyroid nodules, diagnostic yield of fine-needle aspiration (FNA), and their potential for bearing malignancy in GD are still debatable issues. We aimed to determine the prevalence, ultrasonographic and cytological features, and the rate of malignancy outcome of thyroid nodules in a group of patients with GD.

Methods

This was a single center retrospective study. All patients with GD followed up in the Outpatient Clinic of Department of Endocrinology between 2008 and 2013 were included. Thyroid hormone, thyroid autoantibody, TSH receptor antibody (TRAb) levels of all cases during diagnosis were recorded. Basic ultrasonographic data, cytological results of every nodule which underwent fna, and the histopathological data were also recorded.

Results

175 cases (132 females) with mean ± s.d. age 45.9 ± 15.8 were included. 58.8% of the whole group were TRAb positive. 81.1% (n = 142) of the patients were treated with anti-thyroid drugs. 14.3% (n = 25) were finally treated with radioactive iodine with a median (min–max) dose of 12 mCi (5–20). 40% (n = 70) of the cases had totally 134 thyroid nodules. The median (min–max) value of maximum diameter of thyroid nodules was 10.0 (3–54) mm. 14.8% of the nodules owned microcalcifications. 23% (n = 28) nodules underwent FNA. Cytopathology revealed that 24 were benign, two were indeterminate, and the last two were non-diagnostic, both of which were eventually benign in repeat aspirations. The indeterminate nodules went to surgery, which turned out to be benign. Eight additional patients underwent surgery for ablative purposes; only one turned out to be malignant, which was incidental.

Conclusion

Nodular goitre is prevalent in GD. Diagnostic yield of fna may not be so low; malignancy rates do not seem to be high in this group of patients.

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EP993

Thyroid disorders in patients with type 2 diabetes mellitus

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Aim

Increased thyroid volume and thyroid dysfunction (TD) in diabetics have been reported. The aim of this study is to investigate the prevalence of thyroid disorders in patients with type 2 diabetes mellitus in formerly iodine deficient area.

Methods

We included 131 (73 females and 58 males) diabetics without a history of previous thyroid disease and symptoms. The demographic, medical and clinical data, laboratory results (fasting plasma glucose (FPG), HbA1c, lipid profile, TSH, free thyroxine (FT4), and free triiodothyronine (FT3)) were recorded. The result of thyroid function was classified as subclinical hyperthyroidism (Sc-hyper) (TSH ≤ 0.5 mIU/L, FT4 and FT3 normal), euthyroidism (TSH: 0.5–4, FT4 and FT3 normal), and subclinical hypothyroidism (Sc-hypo) (TSH: 4.1–9.9, FT4 and FT3 normal). All participants were evaluated by thyroid ultrasonography (US) and thyroid volume (TV) were calculated by standard formula.

Results

There is a significant difference between females and males with respect to age, smoking habit, and BMI. No significant differences were found between two groups with respect to diabetes duration, FPG, HbA1c, lipid levels, and thyroid function. Sc-hyper, euthyroidism, and sc-hypo were detected in 15 (11.4%), 107 (81.7%), and 9 (6.9%) patients respectively. US findings except TV were similar in two groups. Although, TV was higher in males than females, the diameter of dominant nodule was not different. In all patients, the frequencies of normal US, multinodular goitre (MNG), nodular goitre (NG), diffuse goitre (DG), and thyroiditis with or without nodule were 24 (18.3%), 51 (38.9%), 27 (20.6%), 10 (7.6%), and 19 (14.6%) respectively.

Conclusion

The most common thyroid disorder in diabetics is hypothyroidism. Although, the prevalence of thyroid dysfunction in our patients is concordant with previous results, sc-hyper is more prevalent than sc-hypo. According to our results, 81.7% of diabetics had thyroid gland abnormality by US. In light of these results, all diabetics should be evaluated for thyroid disorders.

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EP994

The occurrence of newly diagnosed thyroid diseases during 13 years follow-up

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The increase in thyroid disease frequency has been observed recently. It may be attributed to the changing iodine status, endemic disruptors, as well as better availability of ultrasound and laboratory tests. The aim of the study was to assess the occurrence of newly recognized thyroid diseases during long-term follow-up.

Material and methods

Study was carried out in 2010–2012 in Krakow area. It included 266 patients aged 23–81 years (168 females and 98 males) out of 548 subjects with no thyroid diseases detected during previous survey (1997–1999). In each patient thyroid ultrasonas was performed, and TSH, FT4, and ATPO levels were assessed.

Results

During 13 years primary hypothyroidism requiring treatment with levotriovxine was detected in 29 subjects (10.9%). In additional 13 cases subclinical hypothyroidism was recognised (4.9%). Elevated titer of ATPO antibodies was detected in 40 subjects (15%). Two subjects had already been treated with radioactive iodine due to hyperthyroidism. The new case of hyperthyroidism was diagnosed in one person during the survey. In two subjects thyroidectomy had been performed during 13 years preceding the study (including one case of differentiated thyroid cancer). In 112 (42.6%) of studied persons (45.5% of females and 38.1% of males) nodular goiter was recognized: solitary nodule in 19.1% and multinodular goiter in 23.7%. In one male papillary thyroid cancer was detected.

Conclusions

During about 10-year follow-up new thyroid pathology may be detected in up to 50% of studied population.

Disclosure

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EP995

E-selectin in women with autoimmune thyroiditis and the relationships with metabolic syndrome

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Autoimmune thyroiditis (AIT) is characterised by infiltration of the thyroid by lymphocytes and other immune cells. Autoantibodies to thyroid-specific antigens:

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thyroglobulin (TG) and thyroperoxidase (TPO) are also produced. The penetration of inflammatory cells into target organ is regulated by cytokines and adhesion molecules expressed on thyroid endothelial cells. E-selectin is one of the selectin family, and is responsible for interaction between leukocytes and endothelium and facilitates the accumulation of inflammation cells in thyroid gland. It is suggested that chronic inflammation and endothelial dysfunction can lead to increased cardiovascular risk and metabolic syndrome (MS) inAIT. Aim To investigate whether AIT is associated with elevated serum levels of E-selectin; to examine relationships between E-selectin, thyroid function, and different risk factors – components of MS.

Materials and methods
Two hundred and fifty-eight postmenopausal, euthyroid women were enrolled into the study. In 76 women AIT was recognised as the presence of elevated at least one of thyroid antibodies (TPO-Ab and TG-Ab) and the presence of typical thyroid sonography. One hundred and eighty-two women without AIT were control group. Anthropometric measurements were conducted (BMI and WHR) and blood pressure was measured. In all subjects were assessed: lipid profile, glucose, TSH, FT4, TPO-Ab, TG-Ab, and E-selectin concentrations. Thyroid ultrasound scan was performed. The diagnosis of MS was performed using AHA/NHLBI criteria.

Results
When we compared AIT women and control group there were no differences in serum E-selectin concentrations. E-selectin was higher in MS for the two groups, but the prevalence of MS was similar. When we analysed all study women, E-selectin positively correlated with BMI, WHR, and negatively with cHDL and FT4. AIT was associated with elevated TSH.

Conclusions
In our study E-selectin was increased in metabolic syndrome, in relationships with obesity, visceral adiposity and lower FT4, but was not related to thyroid autoimmunity.

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EP996
Ultrasound-guided fine-needle aspiration biopsy is an efficient diagnostic tool in thyroid nodules
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Introduction
Thyroid nodules are commonly encountered in clinical practice, the main diagnostic problem being the benign or malignant nature of the nodules. Fine-needle aspiration biopsy (FNAB) is an efficient diagnostic test for evaluating thyroid nodules. Several studies have showed that the use of ultrasound guidance (US-FNAB) improves the diagnostic accuracy of aspiration biopsies in comparison with palpation guidance (P-FNAB).

Patients and methods
We performed a retrospective study to compare the efficacy of US-FNAB of thyroid nodules with that of P-FNAB. Study group included patients referred to Endocrinology Department for assessment of thyroid nodular disease who underwent FNAB by palpation from 2000 to 2001 and under echoguidance in 2005–2006. In order to avoid differences due to nodules size we have selected only palpable nodules in both groups. Thyroid examinations, ultrasound imaging, and aspiration biopsies were performed by the same endocrinologist. Histopathologic and cytologic diagnoses were compared for patients who were operated.

Results
Study sample consisted of 403 patients. P-FNAB was performed in 106 patients (of which 32 underwent thyroidectomy), and US-FNAB in 297 patients (58 operated). Excepting for moderate local pain in some cases, no adverse effects were noticed. Cytologic diagnostic accuracy rate was 83.87 and 90.19% for P-FNAB and US-FNAB respectively. With use of ultrasound guidance, sensitivity (85.71% for US-FNAB and 59% for P-FNAB), positive predictive value (60% vs 40%), and negative predictive value (97.56% vs 92.3%) were increased significantly and the false-negative rate was significantly reduced (14.28% vs 50%).

Conclusions
 FNAB is an essential diagnostic tool in the management of thyroid nodules. US-FNAB improved the cytologic diagnostic accuracy, sensitivity, and positive predictive value and reduced the false-negative rate in comparison with P-FNAB.

Therefore, practice guidelines should universally recommend US-FNAB in the management of thyroid nodules, permitting an accurate preoperative diagnostic and avoiding numerous unnecessary surgical interventions.

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EP997
Two cases with primary thyroid lymphoma developed on the basis of Hashimoto’s thyroiditis
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Introduction
Primary thyroid lymphomas are rare cancers and account 1–5% of all thyroid cancers and 3% of all extranodal non Hodgkin lymphomas (NHLs). We aimed to present cases of thyroid lymphoma encountered in our clinic.

Case 1: A 54-year-old female patient admitted with pain and swollen on the cervical region. In ultrasonographic (USG) thyroid examination, it was found that both thyroid lobes were very large with routh parenchyme consistent with chronic thyroiditis; also there was a solid nodule 23 mm in diameter in left side. In fine-needle aspiration biopsy (FNAB) of thyroid, there were suspicious findings strongly indicating lymphoid hyperplasy. Patient underwent total thyroidectomy. Pathology results were consistent with extranodal (MALT type) marginal zone lymphoma. There were no pathologic findings implicating systemic involvement; patient is still followed-up.

Case 2: A 40-year-old female patient admitted with hypothyroidism. In USG examination of thyroid, it was found that thyroid parenchyme was extensively heterogeneous and there were multiple nodules. FNAB findings were reported as Hashimoto’s thyroiditis and papillary carcinoma. Patient underwent total thyroidectomy and pathology results were considered as morphologic and immunophenotypic findings consistent with extranodal (MALT type) marginal zone lymphoma. Patient underwent radiotherapy. She is in remission and still followed-up.

Discussion
Primary thyroid lymphomas are rare cancers. Hashimoto’s thyroiditis has been found 94% of the primary thyroid lymphoma cases. MALT lymphoma of thyroid has best prognosis with 100% of 5-year survival expectancy. Early diagnosis is important.

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EP998
Factors affecting the efficacy of radioiodine therapy in patients with Graves’ disease
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Introduction
In treating hyperthyroidism in Graves’ disease (GD) patients with 131I-iodine, the optimum activity of radioiodide is yet to be established. We analysed factors affecting the efficacy of 131I radiotherapy in GD patients.

Materials and methods
The analysed group consisted of 362 (80.9% females and 19.1% males) GD patients, of median age 53 (min: 14 and max: 85) years. GD was diagnosed from clinical features, laboratory tests, thyroid USG, and scintigraphy. All patients with orbitopathy (GO) received glucocorticoids to prevent GO exacerbation. Focal lesions were observed in 164 (84% females and 16% males) patients. 131I was applied for the first time in 85.4% of patients; 45.8% received 131I more than once; 6.1% of all patients received it on first onset of hyperthyroidism, while 48.1% received it on first recurrence. The activity delivered was based on clinical
status, thyroid USG-established volume and 24-h $^{131}$I uptake. Ranges of $^{131}$I activity applied were: up to 555, 555–800, and above 800 MBq. Six months post $^{131}$I treatment euthyroidism or hypothyroidism were stated in 72% of patients.

Results
The median thyroid volume was significantly larger in men (30 ml (18.95–52.75) than in women (24 ml (16.1–37)) ($P=0.006$). No significant differences in efficacy related to $^{131}$I activity were stated six months post treatment. In the group of patients treated with lower (<555 MBq) or higher (555–800 MBq) $^{131}$I activity, 76 or 68.5% of patients, respectively, were effectively cured. Presence of focal lesions did not affect the efficacy of $^{131}$I treatment either. In the group of 28 GO patients significant increase of hTRAB level was observed. De novo GO occurred in 1.9% of patients.

Conclusions
The efficacy of $^{131}$I treatment in GD patients evaluated after 6 months was negatively affected by larger thyroid volumes and by anti-thyroid medication.

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**EP999**

Descriptive analysis of a series of 1567 thyroidectomies in Castilla La Mancha and its association with thyroid cancer

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Introduction
We wanted to analyse the descriptive variables of a series of 1567 thyroidectomy patients between 2010 and 2013 and its association with malignancy in our series.

Material and methods
Retrospective, multicentre study done by review of the medical records of 1567 patients who became thyroidectomy between 2010 and 2013 in eight sanitary areas. This is an analysis of clinical and demographic variables.

Results
The percentage of women/men was 82%/18%. The mean age was 51.8 years (s.d. 15). For the following variables, median and IC range were: time tracking: 1 year (0–3); number of visits 3 (2–6); number of scans performed 1 (1–3); and cytological studies 1 (1–2). 60.9% of patients had a family history of thyroid disease. Thyroid cancer in the family: 3.3% of cases (52 patients). Goitre/nodule was incidental in 30.8% of cases. The reasons for surgical indications were: thyroidectomies for compression symptoms 1.92 (1.13–3.29) ($P=0.017$); no size criterion as surgical indication 1.46 (1.03–2.07) ($P=0.037$); cytology as surgical indication 3.15 (2.29–4.33) ($P=0.001$); and no incidental finding 1.46 (1.03–2.07) ($P=0.03$).

Conclusions
In a multivariate analysis to predict malignancy were significant variables with OR: male sex 1.44 (1.023–2.05) ($P=0.010$); surgical indication 3.15 (2.29–4.33) ($P=0.000$); growth as an indication 2.1 (1.23–3.5) ($P=0.006$); non-existence of compressive symptoms 1.92 (1.13–3.29) ($P=0.017$); no size criterion as indication 1.66 (1.13–2.45) ($P=0.011$); no hyperthyroidism 4.06 (1.8–9) ($P=0.001$); and no incidental finding 1.46 (1.03–2.07) ($P=0.03$).

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**EP1001**

Does vitamin D differ among the different thyroid states? A pilot study in Egyptian patients

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Introduction
Vitamin D plays an essential role in calcium homeostasis and bone metabolism, immune modulation, and control of other hormonal systems. Vitamin D deficiency is also common for many reasons. On the other hand, thyroid diseases have widespread systemic manifestations including their effect on bone metabolism.

Aim
To assess vitamin D status among Egyptian patients with different thyroid states: euthyroid, hypothyroid, or hyperthyroid states.

Subjects and method
45 participants (39 females and six males) were divided into three groups: Group 1: (15) euthyroid subject, group 2: (15) hyperthyroid subjects, and group 3: (15) hypothyroid subjects. Diseases and drugs that affect vitamin D were excluded. History taking including dietary habits, sun exposure and clothes and full examination was done. Serum 25-hydroxy vitamin D level by ELISA, ionised calcium, phosphorus, alkaline phosphatase, TSH, free T3, and free T4 were calculated.

Results
The study showed high incidence of vitamin D deficiency among all groups. 21 subjects (46.5%) had vitamin D deficiency (<30 nmol/l). 24 subjects (52.1%) had insufficiency (30–75 nmol/l), and one subject (2.2%) had vitamin D sufficiency. 25-hydroxy vitamin D was significantly different between groups with the level of 25±15.78 nmol/l in group 1, 42.68±20.03 nmol/l in group 2, and 28.46±20.03 nmol/l in group 3. No significant difference between groups as regard serum ionised calcium and phosphorus and alkaline phosphatase ($P>0.05$).

Conclusions
Vitamin D was deficient in the different status of thyroid function. Assessment of vitamin D and replacement might be recommended in patient with thyroid disorder.

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EP1002

Prevalence of thyroid dysfunction in Spain: diabetes study

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Introduction
Thyroid dysfunction is a common health problem. Its prevalence may vary in different populations, and in Spain, it has not been sufficiently studied. The aim of this study was to evaluate the prevalence of thyroid dysfunction (clinical and subclinical) in our country.

Materials and methods
The diabetes study is a national, cross-sectional, population-based survey. Target population: the entire Spanish population > 18 years. Sample: > 5000 subjects in 112 clusters. Participation: 57%. Variables: clinical, demographic, and lifestyle survey, physical examination and blood sampling. Study period: 2008–2010. Specific variables for this study: the concentration of TSH, FT4, FT3, and TPO antibodies was determined by chemiluminescence (Roche) in 4530 subjects. Iodine concentration was measured in an isolated urine sample by the Benotti technique.

Results
The prevalence of treated hypothyroidism, untreated subclinical hypothyroidism and untreated clinical hypothyroidism were 4.2% (95% CI 3.6–4.9%), 4.0% (95% CI 4.0–5.2%), and 0.3% (95% CI 0.1–0.5%) respectively. The prevalence of hyperthyroidism was 0.8% (95% CI 0.6–1.1%) and the prevalence of positive thyroid autoimmunity (TPO > 50 IU/ml) and 7.5% (95% CI 6.7–8.3%). All thyroid disorders were more prevalent in women than in men: hypothyroidism (total) 13.3% (12.0–14.6%) vs 4.8% (3.8–5.7%), hyperthyroidism 1.1% (0.7–1.4%) vs 0.6% (0.3–1.0%), and positive thyroid autoimmunity 10.8% (9.6–12.1%) vs 4.1% (3.2–5.0%) respectively. Hypothyroidism was associated with the presence of positive anti-TPO antibodies (P < 0.001) and elevated urinary iodine levels (P < 0.001).

Conclusions
We report for the first time the prevalence of thyroid dysfunction in a representative sample of the Spanish population.

Disclosure
CIBERDEM, Ministry of Health, Spanish Society of Diabetes. FIS PI11/02755, SAEN.

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EP1003

Presentations and outcome of thyroiditis from an Outpatient Clinic of Endocrinology

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Background
Thyroiditis is ‘the disorder in which there is inflammation of the thyroid gland’. If diagnosed earlier have often good chances of recovery. Limited data is available related to this problem from low income countries and hence there is delay in the diagnosis and management of this important disorder. The objective of the study was to assess the clinical presentations and early outcome of patients presenting with thyroiditis in a tertiary care hospital.

Design/methods
This case series was conducted from December 2013 to September 2014. Patients between 18 and 70 years of age with acute onset of thyroiditis confirmed on thyroid scan or clinical judgment in cases of contraindication of thyroid scan presenting to the outpatient services was included in the study. Pregnant females, psychiatric illnesses, those patients having other chronic illnesses were excluded from the study. Patients were followed for 6 months.

Results
A total of 26 patients with thyroiditis attended the endocrine clinic. Mean age of patients was 41.2 ± 11.12 years. There were 18 (69.2%) females. Clinical presentations (signs) were fever (65.4%), tender neck (23.1%), goitre (19.2%), localised tenderness in neck, and palpable lymph nodes (26.9%). Major symptoms reported were sore throat (69.2%), weight loss (38.5%) whereas upper respiratory tract infection, thyroid pain, tremor, sweating and fever of unknown origin in 26.9% cases. All the patients had raised ESR. Low TSH < 0.4 was seen in 88.5 and 57.7% had raised free T4 > 1.8. Complete recovery was seen in 85.8% patients while 11.5% had early hypothyroidism.

Conclusion
Fever and sore throat were the main presenting features of thyroiditis patients. ESR was raised in all patients. Majority of patients had complete recovery with appropriate management.

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EP1004

Association between fibromyalgia and thyroid autoimmunity

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Fibromyalgia is a disorder characterised by fatigue, generalised body pain and cognitive symptoms, and the aetiology has not been clearly described. Because similar symptoms are frequently found in Hashimoto’s thyroiditis and there is not an optimal response to the treatment of hypothyroidism, the aim of this study, was to determine the prevalence of fibromyalgia in patients with Hashimoto’s thyroiditis, to explain the symptoms and to select the appropriate treatment. This cross-sectional study used the ‘case study’ method and included 100 euthyroid patients with Hashimoto’s thyroiditis that were referred to the rheumatology clinic of Imam Khomeini hospital in 1392. Patients who met the inclusion criteria underwent a physical examination according to ACR 2010 criteria for fibromyalgia. Data collection and analysis was performed using SPSS 22 software. The mean age of the patients was 38.7 ± 11.58 years, and 7% of patients were male. The prevalence of fibromyalgia was 5%. No significant correlation was found between fibromyalgia patients and other variables such as age, gender, marital status, menopause, education, duration of Hashimoto’s thyroiditis, Anti-TPO and TSH levels, and also no correlation was found between the severity of fibromyalgia and these variables. The prevalence of fibromyalgia was not higher than the normal population; thus, musculoskeletal symptoms could not be justified only with fibromyalgia. According to the low number of samples and lack of information on the prevalence of the disease in Iran, further studies using a larger population are recommended.

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EP1005

A case report of Hoffmann’s syndrome

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Introduction
Hoffmann’s syndrome is a rare form of hypothyroid myopathy characterised with muscle hypertrophy, stiffness and wakefulness. Case report

A 43-years-old woman admitted to our hospital with a complaint of fatigue and progressive muscular weakness with cramps and myalgia started 3 months before. Thyroid gland examination was normal. On neurological examination she had proximal and lower limb muscle weakness (3/4) and hyporeflexia. Her calf muscles was hypertrophic. Laboratory investigation reveals increased serum levels of muscular enzymes, dilipidemia severe hypothyroidism. Electromyography (EMG) muscles revealed low amplitude and short duration motor unit action potentials (MUAPs) with early recruitment suggestive of a myopathic disorder. The patient was diagnosed of having severe hypothyroidism with Hoffmann syndrome. I-thyroxine treatment was started (100 µg per day) and dose was elevated 150 µg per day after 2 weeks later. After 1 month therapy her hypothyroid symptoms reduced, pseudohypertrophy of the calf muscles regressed, muscle enzymes were reduced.

Discussion
The characteristic features of Hoffmann’s syndrome include localised or generalised hypertrophy of muscles in addition to muscle weakness, stiffness, cramp and pain as compared to the classic symptoms of hypothyroidism. The CPK is the best biochemical marker of myopathies. Mild to moderate elevation of serum CPK level is seen in 70–90% patients with hypothyroidism indicative
of muscle involvement but does not correlate with the severity of weakness. The clinical presentation and biochemical features might make it a bit difficult for the physician to differentiate it from polymyositis or muscle dystrophies. Hoffman Syndrome has good prognosis if diagnosed earlier and treated appropriately. This case report shows that Hoffman syndrome, though a rare presentation of hypothyroidism has a good prognosis with timely diagnosis and appropriate management. In the differential diagnosis of myopathy with pseudo-hypertrophy, Hoffman’s syndrome should be considered. It is an infrequent cause of myopathy, with good prognosis.

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EP1006
Successful treatment with radiotherapy in a patient who developed severe Graves’-like ophthalmopathy after treatment with pegylated interferon Alpha-2a for hepatitis C
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Introduction
Interferon treatment for hepatitis C has been associated with Graves’-like thyroiditis, developing in rare instances severe ophthalmopathy. The usual management is interferon withdrawal and high-dose corticosteroids, but it may interfere with the resolution of hepatitis. Hereby we report a case successfully treated with radiotherapy, which in our knowledge has never been previously reported.

Case report
A 52-year-old woman was diagnosed of chronic hepatitis C (serotype 1) and began treatment with pegylated Interferon Alpha-2A (Pegasys, 180 μg weekly) and ribavirin (1200 mg per day). After a year, she achieved clinical, biochemical and virological remission and the treatment was withdrawn. In the last month of antiviral treatment, the patient reported symptoms of hyperthyroidism, eyelid swelling and diplopia. TSH was suppressed and free T₄ was 2.27 ng/dl. TC-99 m scintigraphy showed irregular uptake with cold areas. The ultrasonography showed multinodular goiter, and the FNAC was reported as chronic lymphocytic thyroiditis (benign). An orbitary CT scan showed prominent enlargement of muscle and retroorbital fat with exophthalmos. The ophthalmologist recommended high-dose corticosteroid pulses, but we were concerned about the risk of hepatitis recurrence. The patient received standard metimazol treatment for hyperthyroidism and bilateral retro-orbital irradiation with a total dose of 10 Gy fractionated in 1 Gy once a week over 10 weeks. After the seventh session, the diplopia remitted and the patient is presently asymptomatic.

Conclusions
Retroorbital radiotherapy should be considered as an alternative treatment for Graves’-like ophthalmopathy associated to interferon treatment, avoiding the need for high-dose corticosteroids which may result in hepatitis recurrence.

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EP1007
Hypothyroidism in clinical practice
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Hypothyroidism is the most common endocrine disease that was seen in the clinical practice especially for family. What issues about hypothyroidism should be covered in clinical practice? A 36-year-old woman who was diagnosed with hypothyroidism 3 years ago tells her endocrinologist that she wants to conceive in the next year. She was treated with LT₄, 0.1 mg per day. Her last serum TSH was 0.7 mIU/l. She is instructed to notify her endocrinologist as soon as she finds out that she is pregnant so that a serum TSH level can be checked. Her menstrual period is 1 week late, a home pregnancy test is positive, and her serum TSH level is 1.9 mIU/l.

Conclusions
The clinical issues were addressed by clinical scenario followed by questions and stressed on the important clinical points.

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EP1008
Graves’ disease with autoimmune haemolytic anemia
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Introduction
Haematologic involvement is not uncommon in Graves’ disease. Autoimmune haemolytic anaemia is occasionally reported in patients with other autoimmune illnesses. However very rarely reported in Graves’ disease.

Case report
We report a 19-year-old female with reactive arthritis, Graves’ disease and autoimmmune haemolytic anaemia while under treatment with methimazole. Physical examination: Under built female BMI 17, Blood pressure was 110/70, heart rate 100 min., respiratory rate 16 min, temperature 37.6, jaundice, pallor, no cervical, supraclavicular, epitrochlear, axillary, or inguinal lymphadenopathy. The thyroid gland mildly enlarged not nodular no thrill or bruit, proptosis, no lid-lag, or tremor. Lungs were clear and the heart rhythm was regular, accentuated S1, pulmonary component of S2 ejection systolic murmur over the cardiac base no click, or gallop. The abdomen was soft and non-tender, with the liver edge not palpable; the spleen was palpable 3 cm below LF costal margin, joint pain affecting both knees with limitation of movement.

Investigations
Haemoglobin 4.4 g/dl, MCV 107.2, platelet count 193 000, WBC count 4 000, reticulocyte count 23.3% Bilirubin 4.0 mg/dl (direct 0.4), LDH 311 U/l, positive cold agglutinin test, ESR:128, ANA negative. Abdominal sonar mild splenomegally, normal echo cardiology. The patient was started on prednisone 1 mg/kg with rapid improvement in her anaemia and jaundice. 11 days after admission haemoglobin improved to 10.0 g/dl. The prednisone was tapered off over 3 months with continued stable haemoglobin levels and no evidence of recurrent haemolysis.

Conclusion
We report a case of concurrent reactive arthritis, Graves’ disease, and autoimmune haemolytic anemia. Yersinia enterocolitica infection could theoretically cause both reactive arthritis and Graves’ disease, although we cannot prove this connection in our patient’s case which improved dramatically on steroids.

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EP1009
Successful treatment of hypothyroidism with rectal thyroxine can be achieved with variable dose response: a case report
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Introduction
Hypothyroidism is a common endocrine disorder worldwide. Its treatment is with oral thyroxine, but when this route cannot be utilised then intravenous thyroxine is an alternate but not available in some countries so rectal thyroxine administration can be used but clinical experience is lacking.

Case report
This is a case of a 55-years-old Pakistani male known case of hypothyroidism since July 2007 and was maintaining normal TSH and FT₄ level on thyroxine 125 μg per day. He was diagnosed as recurrent laryngeal carcinoma and planned to undergo change of tracheostomy and feeding gastrojejunostomy surgery. As he was unable to take oral referred for hypothyroid medical optimisation prior to surgery. On presentation he was constipated, lathargic had tracheostomy and was on total parental nutrition and not taking his thyroxine for last one month. His TSH was >150uIU/ml and FT₄ was 0.44 ng/dl. As the intravenous thyroxin was not available was started on rectal suppository of thyroxin 250 μg per day. The dose of rectal thyroxine gradually increased to 500 μg per day and his TSH level dropped to 8.83 uIU/ml and FT₄ level raised to 1.29 ng/dl and patient underwent successfully for gastrojejunostomy and started him on thyroxine 125 mcg per day through gastrojejunostomy tube and maintaining normal TSH and FT₄ level.

Conclusion
Patients with hypothyroidism can be managed with rectal thyroxine responses are variable as in our case required four times the oral dose.

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EP1010
1 year response rate to 10 mCi radioactive iodine (I131) in patients with relapsed Graves' disease
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Introduction
Failure of medical treatment in patients with primary diffuse toxic goitre (Graves’ disease) was reported in around 50% of patients and can occur few months after cessation of therapy. Radioactive I131 therapy is a good therapeutic alternative that can be used safely in patients with relapsed Graves’ disease and achieve good response rate with hypothyroidism representing the main side effect.

Aim
The aim of the current study is to assess one year response rate to 10 mCi of I131 in patients with relapsed Graves’ disease post failure of medical treatment patients and methods: 33 patients who had transient control of clinical manifestations with normal thyroid hormonal profile post at least 12 months of continuous proper dose of of neonercazole therapy were included. This was followed by variable period of disease control (range: 7-19 months). After a mean period of 13.4 ± 5.5 months with no thyrotropic clinical manifestations and more importantly normal thyroid hormonal profile during follow up, all patients had clinically and biochemically confirmed thyrotoxic state with a diagnosis of relapsed primary diffuse toxic goiter (relapsed Graves’ disease). All presented for I131 therapy post failure of medical treatment and confirmed relapse. They received 10 mCi of I131 on out patient basis. Patients were followed up for 1 year to assess response to I131 therapy.

Results
14 patients (40.4%) developed clinical hypothyroidism that was confirmed biochemically 3 months post I131 therapy. 1 year post 10 mCi of I131 both clinical and biochemical data showed overt hypothyroid state in 21 patients (63.6%). One patient (3%) with subclinical hypothyroidism was diagnosed by thyroid function tests with no clinical symptoms. Normal thyroid function tests with no clinical manifestations of recurrence were reported in eight patients (24.4%). Considering both hypothyroid and euthyroid states as successful response to I131 therapy, so the overall successful response rate post 1 year of 10 mCi of I131 therapy is 91%. Failure of response to 10 mCi of I131 with a need for a second I131 dose was reported in only three patients (9%).

Conclusion
10 mCi of I131 is a good therapeutic choice in patients with relapsed Graves’ disease with an overall response rate 1 year post I131 therapy of 91%. Hypothyroidism occurs as early as 3 months post therapy in around 40% of patients, increasing to 66.6% by the end of first year after therapy.

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EP1011
Correlation of midkine levels in serum and thyroid nodules with histopathological, haematological and radiological variables
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Aim
To evaluate serum and intranodular vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor-1 (VEGFR-1) level thyroid nodules and explore its relevance to ultrasound feature/pathological results.

Methods
A total of 80 patients (56 women, 24 men) with thyroid nodules were included in this prospective study. Thyroid function tests, fine needle aspiration biopsies, ultrasonographic evaluation were routinely made. In addition, levels of serum and intranodular VEGF, VEGFR-1 were measured. Any possible correlations between serum and intranodular VEGF, VEGFR-1 and biochemical or radiological variables under investigation were sought.

Results
The average age of study group was 51.9 ± 14.4. Both SMK and NMK were found to be higher in hypoechoic nodules with an irregular border and absent halo. Serum MK levels were significantly higher in nodules containing microcalcifications than the macrocalcification or without calcification (P = 0.001). Serum MK levels were high in patients with differentiated thyroid carcinoma, compared to patients with follicular adenoma or nodular hyperplasia. Serum MK levels seemed to correlate with nodular MK levels (r = 0.54, P < 0.001).

Conclusion
Results of the current study showed that both SMK and NMK were indicators of highly malignant/suspicious thyroid cytopathology and also correlate well with sonographic features of thyroid malignancy. We suggest that Midkine may serve as a novel biomarker in conjunction with the cytopathological results in preoperative assessment of thyroid nodules.

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EP1012
Correlation of VEGF, VEGFR-1 levels in serum and thyroid nodules with histopathological and radiological variables
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Aim
To evaluate serum and intranodular vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor-1 (VEGFR-1) level thyroid nodules and explore its relevance to ultrasound feature/pathological results.

Methods
A total of 80 patients (62 women and 18 men) with thyroid nodules were included in this prospective study. Thyroid function tests, fine needle aspiration biopsies, ultrasonographic and scintigraphic evaluation were routinely made. In addition, levels of serum and intranodular VEGF, VEGFR-1 were measured. Any possible correlations between serum and intranodular VEGF, VEGFR-1 and biochemical or radiological variables under investigation were sought.

Results
The average age of study group was 54.1 ± 13.3. Average BMI was 27.6 ± 4.2 kg/m2. There were no statistically significant differences between sVEGF; nVEGF; nVEGR1-1 based on gender (P > 0.05). But serum VEGFR-1 in male was higher than women (P = 0.045). Although nVEGR-1 was significantly higher in normal BMI patients compared with the obese patients (P = 0.02), there were no differences sVEGF; sVEGR-1; sVEGR-1 and nVEGR-1. There were no significant differences between sVEGF; nVEGF-1; sVEGR-1 and nVEGR-1 levels (P > 0.05) according to number of nodules (single and multinodular), benign and malignant ultrasonographic features (large nodules > 4 cm; microcalcifications; intranodular hypervascularity: irregular border; hypoechogenic structure; incomplete thick halo; regional lymphadenopathy). When we grouped patients according to the thyroid status; sVEGF-1 and nVEGF-1 levels were higher in hypothyroid patients than thyroid patients. (P = 0.016). There were no significant differences sVEGF-1; nVEGF-1 and nVEGFR-1 levels between the groups according to scintigraphic sign. But sVEGF was found higher in hyperactive nodules than others. sVEGF, sVEGR-1, nVEGF, nVEGR-1 levels had no significant differences according to thyroid nodule size; (P > 0.05). There were no significant differences between sVEGF; sVEGF-1; nVEGF and nVEGF-1 levels between malignant/suspicious cytolgy and benign cytolgy (P > 0.05). Both sVEGF-1 (r = 0.29; P = 0.008) and nVEGF levels inside nodule (r = 0.29; P = 0.01) was significantly raised with increasing age. nVEGFR-1 was decreased with increasing BMI (r = –0.32; P = 0.004). There was no relationship between nodule size and sVEGF; nVEGF; sVEGR-1; nVEGR-1 (P > 0.05).

Conclusion
As a result; in our study we showed a relationship between sVEGF; nVEGF; sVEGF-1; nVEGF1 levels; and age; gender; BMI; hypothyroidism. The number of malignant or suspicious groups were very small in our study, which is the limitation of this study. Studies which has more number of patients are required to evaluate it.

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Prevalence of short stature in juvenile hypothyroidism and the impact of treatment in tertiary care centre

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Background
Juvenile hypothyroidism is very common problem in developing part of world, and produces various skeletal manifestations and one of them is short stature and it is the most common reason for referral to endocrinologist. It has very wide etiology and one of them is hypothyroidism, which needs special attention, as the treatment impact of thyroxin replacement has favourable outcome.

Aim and objectives
To study the prevalence of juvenile hypothyroidism, to study the various radiological manifestation of juvenile hypothyroidism and to study the impact of treatment on short stature.

Materials and methods
Out of total 900 patients, 87 patients found to be of juvenile hypothyroidism were enrolled in the study that were 6–18 years of age with newly diagnosed or on follow in the OPD of Department of Endocrinology and Metabolism over a period of 1½ years were evaluated clinically and by laboratory tests. Serial assays of TSH, T4, T3 and skeletal X-rays were done and clinical and radiological outcome of patients were analysed.

Statistical analysis
Data were analysed by SPSS version 17 and were presented in the values of mean, median, and percentages. The P-value of <0.05 was considered significant.

Results
The mean age of diagnosis of juvenile hypothyroidism was 11.2 years, and the females had twice the incidence than that of males, the mean TSH value were 118 µIU/ml while T4 and T3 were very low. Marked improvement in the anthropometry was seen in comparison to the initial assessment which was well correlated with the normalisation of the TSH level and the X-ray of the bone. The maximum impact of hypothyroidism was on delayed bone age.

Conclusion
Juvenile hypothyroidism, constituent about 10% of total hypothyroid patients and it is more common than congenital hypothyroidism. The presentations may be varied including short stature, spondyloolisthesis, delayed bone age and irregular ossification of the epiphyses. Prompt recognition of the findings can lead to early and effective treatment, and improving the skeletal defects.

EP1015
The role of circulating sTWEAK in the pathogenesis of Hashimoto’s thyroiditis and its relationship with other cytokines: a pilot study

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Objective
We aimed to investigate the role of sTWEAK in the pathogenesis of Hashimoto’s Thyroiditis (HT) and its relationship with IL-12, IL-17-A and TGF-β1.

Methods
Serum TSH, FT4, anti-TG and anti-TPO were measured and thyroid USG was performed to both group. In addition serum samples were collected and stTWEAK, IL-17-A, IL-12 and TGF-β1 were measured.

Patients
Six patients (20 patients were euthyroid, 20 patients were subclinical hypothyroidism and other 20 were overt hypothyroidism), who were newly diagnosed with HT and did not receive any treatment, and 20 patients with no known disease as the healthy control group were included in the study.

Results
The HT group had lower levels of sTWEAK and TGF-β1, but had higher levels of IL-12 and IL-17-A as compared to the control group. Of these, only the difference between IL-17-A levels reached the statistical significance (2.1 [1.1–10.7] vs 1.8 [1.2–2.3]) P<0.001. The overt hypothyroidism group had significantly higher levels of IL-12 than those of other groups. All of the subgroups had significantly higher levels of IL 17-A than those of control group. sTWEAK was negatively correlated with IL 17-A in the overt hypothyroidism.

Conclusions
We achieved data that support the role of sTWEAK in the pathogenesis of Hashimoto’s Thyroiditis (HT) and its relationship with IL-12, IL-17-A and TGF-β1.
significant relationship between serum selenium levels and nodular thyroid disease was not seen.

Conclusion
Our study was done in a iodine sufficient area. Mean serum selenium levels were lower compared to other studies in Turkey. This condition can be associated with the low selenium content of the soil. Nodular thyroid disease shows multifactorial features. Besides iodine deficiency additional factors such as selenium deficiency can be responsible for the increase of nodule formation. Further studies should be done to assess the role of selenium in the thyroid nodule formation.

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EP1017
Technique of story-telling in Patient care with reference to endocrine surgery
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Background
In the modern day busy clinical practice the communication between patient/relative and care giver is at minimal level. The patients and relatives feel apprehensive when advised about the surgical/interventional treatment. In such situation they feel the need of detail information from the care givers which on many occasions is not available. Story telling is such a technique of health communication made out in common man language which can be made animated and interactive using virtual characters and can operate in a virtual environment eliminating the need of health professionals. We intended to study the efficacy of storytelling technique on patients undergoing Hemithyroidectomy for benign cytology.

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, counseling 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 like Adobe Flash, Photoshop, Captivate, Maya and Final Cut Pro 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.

Result
20 patients filled the questionnaire. 19 found the movie useful and their remaining questionnaire was analyzed. Mean age was 35.45 ± 12.8 years. 15 (75%) were females. All patients were euthyroid. The mean weight was 40.80 ± 20.79 gm. The final histopathology was colloid in majority. In the questionnaire, the mean score for improved understanding of the disease was 73.9 ± 14.7 (P = 0.003), better organization of treatment was 78.6 ± 13.1 (P = 0.000), stimulated interest in the relatives was 70.8 ± 15.8 and saved unnecessary discussion with the consultant was 55.5 ± 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 and relatives in decision making and also saves valuable time of the treating consultant. Future studies with larger numbers are needed.

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EP1018
Adiponectin and gut hormones in thyroid dysfunction: a new concept (PPG axis)
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Background
Integration between fat tissue, gastrointestinal tract, and the brain has attracted scientific interest in recent years. Thyroid hormones influence carbohydrate metabolism and can play a role in obesity development. The relationship between adiponectin and gut hormones such as ghrelin, obestatin and ghrelin has been reported. Numerous studies have demonstrated the role of adiponectin and ghrelin in the regulation of carbohydrate metabolism in humans. However, it is not clear whether the levels of adiponectin and ghrelin reflect the degree of dysfunction in thyroid disease.

The primary aim of this study was to assess the correlation between adiponectin and ghrelin with the degree of thyroid dysfunction.

Methods
The study was performed on 72 subclinical hypo- and hyperthyroidism, and 33 healthy euthyroid subjects. Serum concentrations of adiponectin, ghrelin, obestatin, TSH, free T3 and free T4 were measured by ELSA, ECLIA, IRMA and RIA methods.

Results
Serum levels of adiponectin were decreased in hypothyroids and increased in hyperthyroids (11.91 ± 5.02 and 15.13 ± 5.88 ng/ml, respectively) than the controls (12.73 ± 5.19 ng/ml, P < 0.05). Ghrelin and obestatin values were lower in hypothyroids (320 ± 81 and 44.3 ± 11.7 ng/l, respectively), and higher in hyperthyroids (750 ± 289 and 71.1 ± 27.3 ng/l, respectively, compared to the controls (487 ± 110 and 58.5 ± 10.3 ml/g respectively, P = 0.05). We found a negative correlation between TSH and adiponectin (r = −0.42, P < 0.05).

In addition, ghrelin and obestatin showed strong correlations with TSH (rTSH = −0.53, rT3 = −0.59, P < 0.001). Also, strong correlations were observed between adiponectin and gut hormones (rT3 = 0.78, rT4 = 0.69, P < 0.001).

Conclusion
Our findings show adiponectin and gut hormones are significantly affected by thyroid dysfunction. Additionally, these hormones are noticeably correlated with each other. Hence, we would like to consider a new regulatory concept, as a novel Pituitary-Fat-Gut axis.

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EP1019
A case of unilateral Graves’ disease
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Introduction
Thyroid hemiageneration is a congenital developmental disorder. Most cases are euthyroid although hyperthyroidism, hypothyroidism, and malignancy may develop. We present a case of hemiageneration with Graves’ disease.

Case
A 45-year-old female patient was admitted to the endocrinology ward due to nausea and diarrhoea. She had hyperthyroidism for 1 year. She did not have any family member with thyroid disease. She was already on propylthiouracil therapy. She did not bear signs of Graves ophthalmopathy. Thyroid function tests revealed a TSH level of 0.01 mU/ml (0.35–4.94), free T4 1.80 ng/dl (0.7–1.48), free T3 3.82 pg/ml (1.7–3.71). TSH receptor antibody, antithyroid peroxidase antibody, and anti-thyroglobulin antibody were all positive. Left lobe and isthmus were invisible on ultrasound. Right lobe was 44 × 18 × 12 mm in size with heterogenous hypervascular parenchyme echogenicity containing no nodules. Thyroid scan using 5 mCi of 99mTc showed increased homogeneous tracer uptake in the right lobe (6.7%). Isthmus, pyramidal lobe, and left lobe were not visualised. The patient was diagnosed with thyroid hemiageneration and Graves’ disease. The dose was readjusted and RAI therapy was planned.

Conclusion
In case of unilateral increased uptake on scintiscan Graves’ disease with hemiageneration must be kept in mind in the differential diagnosis of autonomous solitary adenoma, postinflammatory atrophy of thyroid in Hashimoto’s disease, focal or unilateral subacute thyroiditis, and primary or metastatic carcinoma. It is prudent to do thyroid ultrasound along with scintigram.

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EP1020
Evaluation of oxidative stress in patients with euthyroidism and with subclinical hypothyroidism
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Objective
There is not sufficient data about oxidative stress in euthyroid Hashimoto (EH) and subclinical hypothyroid Hashimoto (SHH) disease. We studied oxidative stress with more oxidative stress tests in EH and SHH patients and assessed whether there is an association between Hashimoto disease and PON1 phenotype.

Materials and method
35 EH and SHH patients and 38 control was included to the study. Comprehensive biochemistry, routine blood analysis, total antioxidant status (TAS), total oxidant status (TOS), oxidative stress index (OSI), arylesterase (ARE) paraxonase (PON), lipid hidroperoxide (LOOHs) were measured, and PON1 phenotype was determined.

Results
The levels of TOS and OSI increased significantly in patients with EH and SHH when compared with the control group (for TOS P = 0.005, P = 0.004; for OSI P = <0.001, P = <0.001, respectively). The level of ARE activity increased closely significant in patients with EH, and increase significantly in patients with SHH. The control group had levels of PON, TAS, LOOHs are similar to the control group. Hashimoto’s patients also have found that PON1 phenotype distribution similar to the control group (P = 0.303).

Conclusion
TOS, OSI and ARE were found to be increased in EH patients; however TAS, paraxonase and LOOHs were similar to the control group. Increased OSI is related to increase in TOS in Hashimoto patients, because TAS was found to be similar to the controls. In EH and SHH patients, ARE activity, which is an indicator of molecular concentration of PON 1 enzyme, was found to be increased. On the other hand paraxonase activity was similar to the control group, due to its consumption during the process of reducing the elevated LOOHs as a result of the increase in TOS. Consequently lipid peroxidation was found to be at a similar level with the controls. Oxidative stress parameters and biochemical values are similar in EH and SHH patients. In the PON1 phenotyping we performed, no PON1 phenotype creating predisposition to Hashimoto disease was detected.

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EP1021
Circulating levels of irisin is elevated in patients suffering from hypothyroidism and obesity in Hashimoto’s thyroiditis: original article
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Background and objectives
Our objective in this study was to discover the relationship of irisin hormone, which acts on adipose tissue and the metabolism as thyroid hormones, with the thyroid functions and the obesity secondary to thyroid disease.

Methods
A total of 74 patients were included in the study, of the patients, 37 were newly diagnosed with Hashimoto’s thyroiditis dependent hypothyroidism but not received a treatment yet, and the remaining 37 were healthy volunteers with no known disease. Serum TSH, free thyroxin (fT4), anti-thyroglobulin (anti-TG) and irisin level were identified to be independent predictors in the diagnosis of hypothyroidism (K = 0.255, P = 0.017). The hypothyroidism group had higher median levels of irisin in the obese patients than those in the control group (3.10 ng/ml vs 2.10 ng/ml relatively; P = 0.013). The irisin level was negatively correlated with the age in the entire population and patients with hypothyroidism (r = -0.255, P = 0.028; r = -0.346, P = 0.036 respectively). The irisin level was positively correlated with the TSH (r = 0.247, P = 0.034) but negatively with the anti-Tg (r = -0.316, P = 0.006) in the entire population. Obesity, total-SH, irisin level and anti-Tg level were identified to be independent predictors in the diagnosis of hypothyroidism in the multivariable logistic regression analysis.

Conclusions
To the best our knowledge, this study is the first in literature to identify that obesity, irisin level and anti-Tg level are independent risk factors on hypothyroidism.

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EP1022
The serum irisin level in non-diabetic patients with chronic kidney disease
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Background and objectives
Our objective in this study was to discover the relationship of irisin hormone, which acts on adipose tissue and the metabolism as thyroid hormones, with the thyroid functions and the obesity secondary to thyroid disease.

Methods
A total of 74 patients were included in the study, of the patients, 37 were newly diagnosed with Hashimoto’s thyroiditis dependent hypothyroidism but not received a treatment yet, and the remaining 37 were healthy volunteers with no known disease. Serum TSH, free thyroxin (fT4), anti-thyroglobulin (anti-TG) and anti-thyroid peroxidase (anti-TPO) were measured and thyroid ultrasonography was performed to both group. The serum irisin levels were measured using the commercially available ELISA kit.

Results
The hypothyroidism group had higher levels of irisin compared with the control group (2.77 ng/ml vs 2.15 ng/ml respectively; P = 0.017). The hypothyroidism group had higher median levels of irisin in the obese patients than those in the control group (3.10 ng/ml vs 2.10 ng/ml relatively; P = 0.013). The irisin level was negatively correlated with the age in the entire population and patients with hypothyroidism (r = -0.255, P = 0.028; r = -0.346, P = 0.036 respectively). The irisin level was positively correlated with the TSH (r = 0.247, P = 0.034) but negatively with the anti-Tg (r = -0.316, P = 0.006) in the entire population. Obesity, total-SH, irisin level and anti-Tg level were identified to be independent predictors in the diagnosis of hypothyroidism in the multivariable logistic regression analysis.

Conclusions
To the best our knowledge, this study is the first in literature to identify that obesity, irisin level and anti-Tg level are independent risk factors on hypothyroidism.

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Conclusion
This study examined numerous parameters of OS according to HT stages. The findings provide a general picture of how OS might be affected by thyroid hormone and thyroid autoantibody levels in patients with HT.
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EP1024
The relationship between procalcitonin and thyroid autoantibodies in patients with Hashimoto's thyroiditis

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Background
Procalcitonin (PCT) is often an increased acute phase reactant in the bacterial infection-related inflammation, and its serum level is reported elevated in several autoimmune disease. However, the level of PCT and its relationship with autoimmune remain unknown in Hashimoto's thyroiditis (HT). Our objective was to investigate the serum levels of PCT and its association with autoantibodies in patients with euthyroid HT.

Methods
A total of 80 participants, 40 patients were newly diagnosed with euthyroid HT and 40 healthy volunteers with no known disease. Thyroid function tests and thyroid autoantibodies are analyzed in hormone laboratory with Electrochemiluminescence immunoassay. The serum levels of PCT were measured by ELISA kit.

Results
Hashimoto's thyroiditis patients had higher median PCT levels than those of the control group (34.3 pg/ml vs 27.8 pg/ml respectively; P = 0.037). In the entire population and HT group, the PCT level was positively correlated with systolic and diastolic blood pressures (the entire population; r = 0.320, Z 0.004; r -0.267, P = 0.017; HT; r 0.355, P = 0.025; r 0.420, P = 0.007). PCT and TPO levels were identified to be an independent predictor in diagnosis of HT in the multivariate logistic regression model. An increase of one unit in the PCT level increased the risk for HT by 1.478 times and an increase of one unit in the anti-TPO level increased the risk for HT by 1.164 time when the other risk factors were kept constant.

Conclusion
Procalcitonin being the independent predictor of HT, as indicated in the multivariate regression analysis, suggests that PCT could be a hormone associated with the autoimmunity. Extensive and further researches are needed in this field.
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EP1025
Mimic the symptoms of thyroid disorders in pregnant women

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Introduction
The prevalence of these disorders in pregnant women is relatively high and may affect mother and foetus adversely if they are not evaluated and treated appropriately. Therefore, their diagnosis and treatment is very important. On the other signs and symptoms of thyroid disease can often be masked by the physiologic changes of pregnancy and are not found. The aim of this study was to evaluate the physiological symptoms similar to thyroid disorders and their incidence in pregnant women without thyroid disorders.

Materials and Methods
This study is a population based cross sectional study. A total number of 1600 pregnant women were selected with population based cluster method in prenatal care centres. After questioning the women about the symptoms of thyroid disease and relevant clinical examination, blood samples were taken for thyroid tests and serum T3, T4, TSH, TFT, T3 uptake and TPOab were measured.

Results
63.5% of the participants in this study had normal thyroid function. The prevalence of overt hypothyroidism and hyperthyroidism were 3.8 and 0.8%, respectively and 29.8% of patients had subclinical hypothyroidism. 64.9% of pregnant women without thyroid dysfunction had one or more of the symptoms of thyroid disorders. 24.3% of them had one or two symptoms and 41.5% of them have three or more of the symptoms of thyroid disorders in pregnancy. Most symptoms was laziness and drowsiness (30.3%), followed by fatigue (29.3%). 2.2% of pregnant women have goitre and the symptoms were minimal.

Discussion
The correct planning in order to evaluate and diagnose thyroid disorders during pregnancy is important. Understanding the value and interpretation of thyroid function tests during normal pregnancy is necessary to discriminate between anticipated changes, pathological changes appear.
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EP1026
An unusual clinical presentation of subacute thyroiditis in a patient with Hashimoto thyroiditis

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Hashimoto thyroiditis (HT) is the most common cause of hypothyroidism. Subacute thyroiditis (SAT) is an uncommon disease with characteristic clinical features. Co-existence of HT and SAT is very rare and diagnosis can be challenging.

Case
A 42-year-old woman with HT and multinodular goitre under levothyroxine sodium (LT4) therapy admitted to internal medicine clinic with 1 month history of anterior neck pain radiating to jaw. Thyroid function tests (TFF), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were normal. Neck ultrasonography (NUS) revealed a hypovascular focal area in right lobe (RL) which could be consistent with thyroiditis. However, NUS showed an increase in the size of focal area a week later. She was referred to endocrinology clinic for differential diagnosis (DD). Complaints were consistent with SAT, however TFF, ESR and CRP were normal. LT4 was stopped due to the possibility of thyrotoxicosis in SAT and to perform thyroid scintigraphy (TS). She was anxious and had another NUS by her own will 12 days later. NUS reported further progression of area in RL and formation of a new area in left lobe (LL) with a suspect of thyroid lymphoma (TL). TS revealed decreased LL activity and increased background activity. DD included three rare situations: TL, painful HT and SAT co-existing with HT. Clinical presentation was consistent with SAT, however no inflammatory response and thyrotoxicosis developed. TL is more prevalent in HT but rarely painful. However, rapid progression of NUS findings suggested lymphoma possibility. We performed fine needle aspiration biopsy (FNAB) to exclude TL. FNAB demonstrated giant cells compatible with SAT. During 6 months of follow up thyrotoxicosis was not observed and thyroid stimulating hormone increased gradually. LT4 was initiated again. She refused steroid therapy. HT, an autoimmune disease, can alter the course of SAT and FNAB may be required for DD.

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**EP1027**  
**Association between thyroid specific genotypic variation and phenotypic expression of dyshormogenetic goitre and Hashimoto’s thyroiditis in children and adolescents: a South Indian experience**  
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**Conclusions**
was 22.95.

**Material and methods**
Blood samples were collected from 20 patients with dyshormogenetic goiter (DH) and Hashimoto’s thyroiditis (HT). Genomic DNA was extracted from peripheral blood leucocytes. PCR and direct sequencing were used to analyse for NIS, DUOX2 and TPO genes. Detailed clinical, biochemical and follow-up data were recorded in a structured proforma. Subjects with hypothyroidism were treated with thyroxine replacement. Detailed genetic analysis with 142 SNP (single nucleotide peptides) and eight sets of primers were done.

**Results**
The age of the cohort was 11±4.5 (5–17) years. F:M ratio was 17:3. The type of hypothyroidism was overt and subclinical in 14 and six patients respectively. Family history of hypothyroidism was present in seven patients (35%). Genetic analysis shows that heterozygous NIS mutations were seen in five children with HT and in two children with DH. A homoygous mutation was picked up in a child with HT. No mutations were found in DUOX and TPO genes.

**Conclusions**
NIS gene mutations appears to be most prevalent mutations in HT and DH amongst South Indian children in this study. The iodine deficiency and ethnic factors may be responsible for this pattern. Further studies are needed to characterise hypothyroid phenotypes in children.

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**EP1028**  
**Evaluation of unknown thyroid disorders in nursing home people**  
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**Introduction**
The prevalence of thyroid diseases increase with age. Mostly, they are undiagnosed. The lack of overt clinical appearance of hypo-hyperthyroidism in elderly people increases the need for an attentive clinician to suspect and investigate for their presence. Thyroid dysfunctions, especially subclinics, are more frequently seen in older populations, have been linked to increased morbidity and mortality. Therefore, elderly people should evaluate in terms of thyroid functions.

**Materials and methods**
Hundred and ninety-two participant were enrolled in the study, 108 of them from the selected nursing home and 84 of them were living in their own home. All of the participants were evaluated in terms of thyroid functions, thyroid ultrasonography and osteoporosis.

**Results**
The nursing home participant (NP) group had 89.8% euthyroid, 3.7% subclinical hypothyroidism, 0.9% overt hypothyroidism, 0.9% overt hyperthyroidism and 4.6% subclinical hyperthyroidism, in household participants (HP) group’s rates were 83.3, 9.5, 0.0, 0.0 and 7.1% respectively. NP group had 64.2%, HP group had 78.3% thyroid nodule. NP group’s osteoporosis ratio was 34.7%, HP group’s was 22.95.

**Conclusions**
There was no statistical difference between two groups in terms of distribution of thyroid dysfunction, thyroid nodules and osteoporosis.

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**EP1029**  
**Thyroid switching and D272E polymorphism**  
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**Introduction**
Graves’ disease and Hashimoto’s hyperthyroidism are common thyroid diseases. However, occurrence of both clinical disorders one after the other in the same patient, is not common.

**Case report**
In this article, we presented two hypothyroid patients who developed clinical thyrotoxicosis during levothyroxine treatment. Both patients were treated with levothyroxine for a long time. Due to occurrence of clinical hyperthyroidism, levothyroxine treatments of the both patients were terminated. Although unmedicated follow-up for about 6 weeks period, recovery from thyrotoxicosis wasn’t observed. Both of the patients were positive for TSH receptor antibody.

**Results**
They were diagnosed as Graves’ disease on the basis of clinical signs, laboratory findings and imaging techniques, then antithyroid treatment was initiated. In both cases, TSH receptor gene sequence analysis was performed, and in both of the patients D272E homozygous polymorphism was obtained.

**Conclusions**
In hyperthyroid cases with the history of hypothyroidism, switching between hypothyroidism and hyperthyroidism should be kept in mind and due to D272E polymorphism, and the other TSH receptor gene mutations, if it is possible genetic analysis should be performed.

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**EP1030**  
**Relationship between thyroid function tests and all-cause mortality in patients on peritoneal dialysis: a prospective analysis**  
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**Background**
Alterations in thyroid function tests results in patients on peritoneal dialysis (PD) might represent a risk factor for cardiovascular disease (CVD) and mortality.

**Objective**
To investigate the relationship of serum TSH, free thyroxine (FT4), and triiodothyronine (T3) concentrations with incident CVD and mortality in PD patients.

**Methods**
Prospective study including all patients attending our PD unit between 2003 and 2012 who had remained at least for 3 months in the PD program. All patients were followed until death, exit of PD program, loss of follow-up, or census date (September 2012). Survival time was estimated by the Kaplan-Meier method. Unadjusted and multivariate Cox regression models were used to assess the effects of several variables on the risk of death.

**Results**
From 169 subjects included in our program, 139 (81.8%) were euthyroid, 4 (2.4%) had overt hypothyroidism, and 26 (15.4%) had subclinical hypothyroidism. Patients in the first tertile of T3 (<0.91 ng/ml) had a higher percentage of CVD events during follow-up (10.9%) than those in the second (0.91–1.10 ng/ml, 1.9%) and third tertiles of T3 (≥1.10 ng/ml, 1.9%, P < 0.05). All-cause mortality was higher in patients in the first tertile of T3 (20%) in comparison with patients in the second (3.8%) and third tertiles (5.6%, P < 0.05). Kaplan-Meier analysis showed that median survival time for all-cause mortality were significantly lower in patients in the first tertile of T4 (P = 0.013). Unadjusted Cox regression analysis showed an increase in the risk of death in patients in this tertile (HR, 4.3; 95% CI, 1.48–12.45, P = 0.007). In the multivariate (adjusted) analysis, this risk of death remained significant (HR, 3.14, 95% CI, 1.05–9.43, P = 0.041).

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Conclusions
Thyroid function tests alterations are associated with long-term incidence of CVD and mortality in uremic patients undergoing PD. In particular, low T3 levels are significantly related to all-cause mortality in this population.
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EP1031
Role of regulatory T cell and CTLA-4 gene as risk factor relapse in Graves’ disease
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Introduction
Graves’ disease (GD) management in Indonesia are generally preceded by administration of antithyroid drugs. Antithyroid drug delivery requires a long time to achieve remission, even more than 50% of patients who had remission can recur after antithyroid medication is stopped. The purpose of this study was to determine the role of CTLA-4 gene and regulatory T cells against recurrence in patients GD in Indonesia.

Methods
The study was conducted using a case-control in 144 patients GD, comparing patients who relapse and recurrence. Definition of relapse if the patient is declared remission after antithyroid treatment for at least 18 months, but relapsed after 12 months of antithyroid medication is stopped. Examination of CTLA-4 gene polymorphism of exon1 by the method of PCR RFLP, and the number of regulatory T cells was checked by flow cytometry.

Results
Research shows that patients with GD have higher risk of relapse if they have family history (P=0.01), degree two of ophthalmopathy (P=0.01) and enlargement of the thyroid gland exceeded the lateral edge of the sternocleidomastoideus muscle (P=0.044). GD patients with polymorphisms of CTLA-4 gene exon1 genotype GG and GA have higher risk of relapse than the AA genotype (P=0.003 and OR=6.545). The number of regulatory T cells in patients with relapsed is lower than non-recurrence (P<0.005). GD patients with the G allele in the gene CTLA-4 exon1 has had lower regulatory T cells than the A allele (P<0.005).

Conclusion
The risk of relapse in patients with GD can be determined prior to administration of antithyroid therapy based on clinical factors, genetics and immunology.
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EP1032
Iodine supplementation to pregnant women is scarcely available in Brazil
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Introduction
A woman’s iodine requirements increase substantially during pregnancy to ensure adequate supply to both mother and fetus. The deficiency of this element may cause several maternal-fetal repercussions. For this reason, iodine supplementation for pregnancy has been recommended and the World Health Organization (WHO) commends an iodine urinary concentration at a median UIC 150–249 μg/l. As in many other countries around the world, there is evidence of iodine deficiency among Brazilian pregnant women. In fact, a recent study identified UIC below 150 μg/l in 57% of the pregnant women investigated. Iodine supplements availability have not yet been evaluated in the country and our objective was identify the availability of dietary supplements for pregnant women in Brazil and verify the amount of iodine present on them, correlating it with the new global recommendations.

Methods
We used our national health electronic system (Anvisa’s Bula ´rio Eletroˆnico) to investigate the nutritional information of dietary supplements used by pregnant women through their package insert. Further, we contacted the pharmaceutical industries and consulted the Brazilian Dictionary of Pharmaceutical Specialties (DEF) 2012–2013.

Results
There are, currently, 23 dietary supplements for pregnant women in use. Based on daily iodine intake recommended by American Thyroid Association, European Thyroid Association and WHO (minimum of 150 μg/day), 52.2% out of these products contain no iodine; 13.0% contain insufficient amounts of iodine (1–149 μg); and only 34.8% contain the recommended quantity of this element.

Conclusion
Despite salt iodination, recent data indicate that at least half of Brazilian pregnant women present iodine insufficiency, reinforcing the need of iodine supplementation during the prenatal period. However, the present study indicates that just one third of the commercially available dietary supplements currently used by Brazilian pregnant women contain the internationally recommended daily iodine intake.
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EP1033
Is there any effect of the treatment on MVP in patients with hyperthyroidism and hyperthyroidism?
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Introduction
In this study, we aimed to reveal the mean platelet volume (MPV) change with treatment in patients with hyperthyroidism and hyperthyroidism. Materials and methods Two groups were retrospectively evaluated as 200 patients (21 male, 179 female) with hyperthyroidism and 200 patients (26 male, 174 female) with hyperthyroidism. Before and after treatment in the outpatient follow, MPV values were compared. Results There is significant difference between MPV values before (8.8±6.1–12.1), 8.7±6.1 (6.7–13.1) and after (9.1±6.1 (7–14), 9.1±6.1 (6–12)) treatment in hyperthyroidism and hyperthyroidism groups respectively and also MPV values increased in both groups after treatment (P=0.001). Conclusion The reason for the changes in MPV in our study can be explained in terms of the effect of the treatment on inflammatory period.
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EP1034
Triiodothyronine is independently associated with metabolic syndrome in euthyroid middle-aged subjects
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Introduction
Recent studies have shown associations of thyroid hormone levels with metabolic syndrome (MetS) among euthyroid individuals, though there have been some inconsistencies. We evaluated the relationships between thyroid hormones and MetS in euthyroid middle-aged subjects in a large cohort.

Methods
Retrospective analysis of 13,496 euthyroid middle-aged subjects who participated in comprehensive health examinations was performed. Subjects were grouped according to TSH, total triiodothyronine (T3), total thyroxine (T4), and T3/T4 ratio quartile categories. We estimated the odds ratios (OR) for MetS according to thyroid hormone quartiles using logistic regression models, adjusted for potential confounders.

Results
Twelve percent (n = 1664) of the study subjects had MetS. Higher T3 levels and T3/T4 ratio were associated with unfavorable metabolic profiles, such as higher BMI, systolic and diastolic BP, triglycerides, fasting glucose and HbA1c, and lower HDL cholesterol. The proportion of participants with MetS increased across the T3 quartile categories (P for trend <0.001) and the T3/T4 ratio quartile categories (P for trend <0.001). The multivariate-adjusted OR (95% CI) for MetS in the highest T3 quartile group was 1.249 (1.020–1.529) compared to the
lowest T3 quartile group, and that in the the highest T3-T4 ratio quartile group was 1.458 (1.141–1.863) compared to the lowest T3-T4 ratio quartile group, even after adjustment for sex, age, body fat percentage, smoking, and HOMA-IR.

Conclusions

Serum T3 levels and T3-T4 ratio are independently associated with MetS in euthyroid middle-aged subjects. Longitudinal studies are needed to define this association and its potential health implications.

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EP1035

Hypothyroidism related to blocking TSH receptor antibodies after allogeneic haematopoietic stem cell transplantation

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Besides total body irradiation and immunosuppressive drugs, massive iodine supply and stress might participate in thyroid dysfunction, described in 50% of allo-HSCT. We report on a rare case of hypothyroidism related to blocking TRAb. A 55-year-old man was admitted for asthma, dyspnea, dysmigia, 8 kg-weight gain, constipation, dry skin, hoarse voice, recent deafness. He had moon face without any goiter. He had received, 1 year before, an unrelated 9/10 human leukocyte antigen matched allo HSCT for acute myeloid leukemia after chemotherapy including antilymphocyte serum and had achieved full female donor chimnism. He developed an acute graft-vs-host disease (GvHD) grade II 1 month post-transplantation treated with cyclosporine. Laboratory tests showed high blood cholesterol (3.53 g/l–n: 1.5–2.4), triglycerides (2.70 g/l–n: 0.3–1.50), CPK (262U/l–n<195), TSH (99 mIU/l;n<3.5) levels as well as antithyroid peroxidase (179 U/ml; n>5) and TSH receptor antibodies (TBII: 102 U/l; n<1) levels with undetectable FT3 and anti-thyroglobulin antibody. The functional study of TBII confirmed high blocking (TRAbs 92%; n<30) and low stimulating (TSAbs 58%; n<1.25) activities. The immunophenotype showed a lymphopenia with an increased CD4+ (48.7%; n: 38–46) and low CD8+ (28%; n: 31–40) percentages. Indeed, the development of autoimmune hypothyroidism is frequent post allo-HSCT and requires regularly monitoring of TSH, given the difficulty of diagnosis in patients whose complaints can easily be attributed to the causal disease or GvHD. Immunological dysregulation during T-cell engraftment may also favour hyperthyroidism, sometimes preceded by a hypothyroid episode related to blocking TBII, called immune reconstitution syndrome. This rare and delayed syndrome has been reported in children post allo-HSCT (Sinha Thyroid 2013) or HIV (Sheik AIDS 2014) treatment and coincided with a rapid adjustment for sex, age, body fat percentage, smoking, and HOMA-IR.

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EP1036

Prevalence of hypothyroidism in a large series of adult thalassemic patients

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Hypothyroidism has been traditionally described as a frequent endocrine complication of thalassemic children: in these patients hypothyroidism is mainly of primary origin and not linked to autoimmunity (Mariotti et al., Pediatric Endocrinol Rev 2011). Fewer data are available on the prevalence and nature of this complication in adult age thalassemia. Therefore, we elected to evaluate thyroid function and autoimmunity in a large series of adult patients.

Study

 Nineteen-five adult thalassemic subjects (48 women and 47 men, mean age 38.1±6.9 years) underwent assessment of thyroid function (FT3, FT4 and TSH) and thyroid autoimmunity (anti-thyroid peroxidase and anti-thyroglobulin antibodies). Serum ferritin was also measured in all patients, who were regularly taking iron-chelating drugs. Hormone deficiencies other than hypothyroidism were adequately replaced.

Results

Thirty-one patients (32.6%), 16 men and 15 women, aged 39.5±6.7 years, turned out to be affected by hypothyroidism. Two of them had previously undergone-thyroid surgical removal for multinodular goitre and carcinoma, respectively. The stratification by age of the other hypothyroid subjects disclosed a prevalence of 25% (2/8) among those aged 20–30, 27.6% (10/37) among those aged 30–40, and 36% (16/44) among those aged 40–50. No hypothyroid patients displayed anti-TPO or anti-TG antibodies. No cases of secondary hypothyroidism were observed. Mean serum ferritin was not significantly different between hypothyroid and euthyroid thalassemic subjects (1067.7±664.5 vs 868.0±743.5 ng/ml, NS, respectively).

Conclusions

Hypothyroidism, primary in all cases, was highly prevalent in our series, being present in one third of the patients. This endocrine complication was equally distributed among genders and its prevalence appeared to progressively increase with age. Since measurement of serum ferritin expresses an estimation of the current degree of iron overload and not its evolution within the clinical history of patients, our data cannot rule out a contribution of secondary hemosiderosis to the pathogenesis of hypothyroidism in thalassemia.

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EP1037

Thyroideectomy: analysis of 184 cases in a single centre

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Aim

To evaluate whether differences exist in terms of patient, radiological, tumour characteristics and surgical complications between malignant and benign thyroidecytectomy.

Materials and methods

184 correlatives cases of thyroidecytectomy during the period from October 2011 to October 2013 are analysed. Patient, ultrasound, tumour and complication characteristics are compared. Categorical data are reported as percentages. Characteristics between the two groups are compared using a Student’s t-test for continuous variables and a Fisher’s exact test or a χ² test for categorical variables.

Results

A female: male ratio of 5:1 (157 women: 28 men) is found with eight malignant cases (28.6%) in men and 35 (22.3%) in women. Malignancy is associated with family cancer history (RR: 0.3 (0.183–0.143), and larger tumour size with benignity. Benignity nodules are 1, 21 cm larger than malignity nodules (P 0.00 (0.474–1.567). No statistically significant differences in terms of age, mean operative time, mean postoperative hospital stay and surgical complications are found.

Conclusions

The nodule size is not an accurate predictor of thyroid cancer. Malignant thyroidcytectomy is not associated with more surgical complications or post-operative hospital stay.

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EP1038

IL-2, IL-4, IL-5, IFN-γ and TNF-α levels in Turkish patients with Hashimoto’s thyroiditis

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**Background**
Hashimoto’s thyroiditis (HT) is one of the most common autoimmune thyroiditis that characterised by lymphocytic infiltration and thyroid hormonal disturbances. Genetic and environmental factors play a role in etiology of the disease, but genetic factors are most common. In this study, we investigated the association between Hashimoto’s thyroiditis and IL-2, IL-4, IL-5, TNF-α and IFN-γ levels.

**Methods**
We performed a case-control study that included 139 cases with HT (50 euthyroid, 50 subclinical hypothyroid, 39 overt hypothyroid patients) and 50 healthy control. Subjects were collected from Endocrinology Clinic of Pamukkale University in Turkey. Serum levels of glucose, insulin, PTH, Ca, phosphorus (P), alkaline phosphatase (ALP) were measured and IL-4, IL-5, TNF-α, IFN-γ analysis were performed with ELISA.

**Results**
IL-2, IL-4, TNF-α and IFN-γ levels were significantly higher in Hashimoto’s thyroiditis patients, there were no significant differences between the groups regarding IL-5 levels. There were no significant differences detected in PTH, ALP and Ca levels.

**Conclusion**
Because of the HT is an inflammatory disease significantly high IL-2, IL-4, TNF-α and IFN-γ level were observed in HT. Practitioners should take into consideration IL-2, IL-4, TNF-α and IFN-γ levels in HT diagnosis. These inflammatory markers may have an important role in the pathogenic pathway in HT.

**Disclosure**
Grant numbers 2012 TFP6.

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**EP1039**

**Descriptive analysis of the histopathological findings of a series of 1567 thyroidectomies**

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**Introduction**
We wanted to analyse the pathology results of thyroidectomies performed in the hospitals of Castilla La Mancha (Spain) between the years 2010 and 2013, inclusive.

**Material and methods**
A retrospective, multicentre, descriptive study of the histopathological results of the 1567 thyroidectomies performed in the hospitals of the eight health districts in our region between the years 2010 and 2013.

**Results**
The histopathological results were benign in 1124 cases (cystic goiter/adenomatous 42.7%, follicular adenoma 9.7%, Hurthle cell adenoma 2.7%, Graves’ disease 2.6%, lymphocytic thyroiditis 7.7%, thyroiditis de Quervain 0.1%, thyroid cyst 0.4%, normal thyroid 0.4%, and other 5.6%) and malignant in 402 cases (papillary microcarcinoma 7.5%, macropapillary carcinoma 14.9%, follicular 1.5%, medullar 1.5%, anaplastic carcinoma 0.1%, parathyroid carcinoma 0.1%, and other 0.3%), and unknown in 2.6% of cases.

**Conclusions**
During the years 2010–2013 1567 thyroidectomies were performed in the hospitals of Castilla La Mancha. In 1124 cases (71.7%) the histopathology was benign and in 402 cases (25.6%) malignant. The most common tumour was papillary carcinoma.

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**EP1040**

**Sensitivity and specificity of thyroid cytology in the diagnosis of malignancy: results of a series of 1567 thyroidectomies**

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**Introduction**
Sensitivity and specificity of thyroid cytology in our series of thyroidectomies were evaluated.

**Material and methods**
A retrospective, multicentre study of 1567 thyroidectomies performed in the eight hospitals of Castilla La Mancha (Spain) during the years 2010–2013.

**Results**
The cytological results were benign in 37.6% of cases, malignant or suspicious of malignancy in 17.3% (10 and 7.3% respectively). In 4.1% of cases the cytology was atypical or indeterminate and in 12.5% follicular proliferation/follicular lesion. There were 8% non-diagnostic cytologies. In patients whose prequirurgical FNA was nondiagnostic, 20.6% had a carcinoma. Overall, 25.6% of patients had thyroid carcinoma. The sensitivity and specificity of suspicion of malignancy or malignant thyroid cytology for the diagnosis of malignancy was 75.8 and 90.3% respectively. There were 3.5% false positive and 4.5% false negative results.

**Conclusions**
Thyroid cytology is the diagnostic technique of choice for the study of thyroid nodule. The results in terms of sensitivity, specificity and nondiagnostic cytology in our series are acceptable.

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**EP1041**

**Surgical treatment of thyroid disease: descriptive analysis and histopathology of a series of 92 cases**

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**Introduction**
Retrospective study of patients undergoing thyroid surgery at the Hospital Virgen de la Luz, Cuenca (Spain) during the years 2010–2013.

**Material and methods**
We evaluated data of 92 patients basically with nodular thyroid disease, who were studied and treated in our hospital.

**Results**
Our series is made up of 92 patients (25% men and 75% women) with an average age of 52 years. The most common form of presentation (47.8%) was recent surgical treatment is emerging thyroid nodule, having less than a year. In 19 cases (20.6%) it was found incidentally, mainly by ultrasound. In most cases, 58 (63%), monitoring prior to surgery was ≤1 year. Ultrasonic findings showed mostly mixed multiple nodules (32.6%). The results of cytology were nondiagnostic in 7.6%, 35.9% benign, atypical 2.2%, 9.8% follicular proliferation, suspicious of malignancy 6.5%, and 10.9% malignant. In 25 cases (27.1%) was not done FNA. In 86.9% thyroid function was normal. Total thyroidectomy was performed in 78.3%, in 20.6% hemithyroidectomy and bilateral subtotal thyroidectomy in 1.1%. Surgery was performed in 65% of cases by the most experienced surgeon. The pathology was benign in 70.6% and malignant in 29.3% cases.

**Conclusions**
The most common presentation in our thyroid disease amenable to surgical treatment is emerging thyroid nodule. In 20.6% of cases it was an incidental finding. Total thyroidectomy was the technique of choice (78.3%), 29.3% of the cases presented a thyroid carcinoma.

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**EP1042**

**Iodine nutritional status among adolescent girls in Uttarakhand State, India**

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**Introduction**
Iodine is an essential micronutrient. Iodine deficiency (ID) among adolescent girls could lead to ID amongst the newborns as they are the future mothers. Uttarakhand state is a known endemic region for ID.
Objective
The present study was conducted with an objective to assess the iodine nutritional status amongst adolescent girls in districts: Udham Singh Nagar (USN), Nainital (N), and Pauri (P) of Uttarakhand state.

Methods
In each district, 30 clusters (schools) were identified by utilising population proportionate to size (PPS) cluster sampling methodology. In each school, 60 girls aged 12–18 years attending the schools were included. A total of 5430 girls from USN (1823), N (1811), and P (1796) were studied. Clinical examination of thyroid of each girl was conducted. From each cluster, on the spot urine and salt samples were collected from 20 girls.

Results
Total goitre rate (TGR) was found to be 6.8% (USN), 8.2% (N), and 5.6% (P) respectively. Median urinary iodine concentration (UIC) levels were 250 μg/l (USN), 200 μg/l (N), and 183 μg/l (P) indicating adequate iodine status amongst the study population. The percentage of families consuming salt with iodine content of <15 p.p.m. was 59.5 (USN), 44.0 (N), and 46.7 (P) percent.

Conclusion
Findings of the present study documented that adolescent girls had adequate iodine nutritional status in three districts of Uttarakhand.

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EP1043
Ultrasoundographical features and cytological findings of thyroid nodules in patients with Hashimoto’s thyroiditis
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Introduction
It is unclear whether ultrasonographic (US) findings and fine-needle aspiration biopsy (FNAB) results of nodules accompanied with Hashimoto’s thyroiditis (HT) are affected by the presence of thyroiditis or not. In this study, we compared US features and cytological results of nodules in patients with and without HT.

Methods
Patients who underwent FNAB in our clinic were evaluated prospectively. Nodules in patients with and without HT were categorised as groups 1 and 2 respectively. Cytological results were classified as benign, atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), follicular neoplasia suspicion, malignancy suspicion, malignant, and nondiagnostic.

Results
181 (35.5%) patients with HT and 329 (64.9%) without HT were included in the study. There were totally 800 nodules, 288 (36%) in group 1 and 512 (64%) in group 2. Ultrasoundographically, presence of hypoechoic halo and marginal irregularity were similar in two groups (P = 0.12 and P = 0.20 respectively). Microcalcification was present in 11.8% of nodules in group 1 and 20.3% in group 2 (P = 0.002). Macrocalcification was detected in 19.5 and 23.8% of nodules in groups 1 and 2 respectively (P = 0.01). 30.6% of nodules in group 1 was hypochoic, 66.3% was isoechoic, and 3.1% was hyperechoic. In group 2, 40.2% was hyperechoic, 58.4% was isoechoic, and 1.4% was hyperechoic (P = 0.01). Solid texture was observed in 78.1% of nodules in group 1 and 62.3% of nodules in group 2 (P < 0.001). Cytological results were as follows; in group 1, 78.1% benign, 2.4% AUS/FLUS, 0.3% malignancy suspicion, 1.7% malignant, and 14.6% nondiagnostic; in group 2, 81.4% benign, 2.3% AUS/FLUS, 0.4% follicular neoplasia suspicion, 1.0% malignancy suspicion, 1.4% malignant, and 13.5% nondiagnostic (P = 0.78).

Conclusion
Suspicious US features such as microcalcification, macrocalcification and hypoechoic appearance are found with a lower prevalence in nodules accompanied by HT. Cytological results were similar in patients with and without HT.

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EP1044
Usefulness of the assessment of thyroid blood flow as a predictor of relapse of Graves’ disease
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Objective
We investigated the clinical usefulness of thyroid blood flow measurement by colour-flow Doppler ultrasonography in predicting relapse of Graves’ disease (GD).

Patients and methods
In 30 euthyroid GD patients, (eight males and 22 females), aged 17–68 years (mean 43.8 ± 12.8), after at least 1 year of treatment with anti-thyroid drug (ATD) and just before its withdrawal, we evaluate with colour-flow Doppler ultrasonography the colour-flow Doppler mapping (the amount of flow was classified on four point scale, 0–3) and we calculate, in pulsed Doppler mode, the peak systolic velocity in the inferior thyroid artery (ITA–PSV). All ultrasound examinations were performed by the same endocrinologist expert in thyroid ultrasound using a duplex Doppler apparatus (Logic Scan 64, B-Side Medical System) with an 8 MHz linear array probe. Clinical data was collected and measurements of TSH, serum free thyroxine, and TSH receptor antibodies were performed. GD relapse was defined as an increase in the serum level of FT4 to above the normal upper range and suppression of serum TSH in 18 months after removal of ATD. Mann–Whitney U test and Fisher’s exact test were used for statistical analysis. The sensitivity and specificity were calculated using a 2 × 2 table.

Results
In relapse group (n = 14, 47%) ITA–PSV was significantly higher than in the non-relapse group (n = 16), (48.5 ± 17.7 cm/s vs 32.6 ± 9.5 cm/s, P = 0.01). For prediction of GD relapse, the best cut-off value was 35 cm/s for ITA–PSV. Sensitivity was 71%, specificity 87%, positive predictive value 83%, and negative predictive value 78%. All patients with grade 3 in colour-flow Doppler mapping (n = 3) had an early relapse of GD (before the first 6 months).

Conclusions
Colour-flow Doppler mapping study and measurement of ITA/PSV in euthyroid GD patients immediately before withdrawal of ATD may assist in the prediction of GD relapse.

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EP1045
The effect of anti-TNF therapy on thyroid function in patients with inflammatory bowel disease
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Introduction
Inflammatory bowel disease (IBD) has been associated with various disorders of thyroid function. Many of these patients are now treated with biological agents targeting on TNF-a.

Aim
To investigate thyroid function in patients with IBD and the potential effect of anti-TNF therapy.

Patients and methods
We studied 41 patients with IBD (25M/16F, 36.4 ± 11 years), without any known thyroid disorder. Eighteen patients (9M/9F, 33.6 ± 8.8 years) were on anti-TNF therapy for more than 1 year, while 23 patients (16M/7F, 38.7 ± 12.5 years) were treated with azathioprine and mesalazine (Aza/Mes). Nine patients from the second group were then treated with anti-TNF and studied again 6 months later. We assessed thyroid function by measuring T3, FT4, TSH, anti-TG, and anti-TPO levels.

Results
One patient presented with clinical and one with subclinical hyperthyroidism. Thyroid auto-antibodies were positive in 12.2% (one anti-TG and four anti-TPO). Patients from the anti-TNF group had reduced levels of FT4 (1.09 ± 0.15 ng/dl vs 1.38 ± 0.9 ng/dl, P = 0.042), with no differences in T3 levels (1.8 ± 0.28 nmol/l vs 2.02 ± 1.7 nmol/l) and TSH (1.76 ± 0.8 mIU/ml vs 1.58 ± 0.9 mIU/ml, P > 0.05).

The percentage of patients with positive thyroid auto-antibodies were lower in the
anti-TNF group, 5.6% (1/18) vs 17.4% (4/23), but without statistical significance (P > 0.05). In patients who were treated for 6 months with anti-TNF, we found statistically significant reduction in FT4 (1.24 ± 0.26 ng/dl vs 1.11 ± 0.16 ng/dl, P = 0.048), without changes in T3 (1.5 ± 0.43 nmol/l vs 1.8 ± 0.2 nmol/l) and TSH (1.82 ± 1.28 mU/ml vs 1.68 ± 0.96 mU/ml), in all comparisons P > 0.05. There was no change regarding thyroid auto-antibodies.

Conclusions

Patients with IBD showed high percentage of thyroid autoimmunity, while the functional thyroid disorders presented were clinical and subclinical hyperthyroidism. Treatment with anti-TNF resulted in reduced levels of FT4, without changes in T3, TSH, and thyroid auto-antibodies.

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Hypo- and hyperthyroidism: causes of hepatic dysfunctions

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Background and aims

The aim of this study is to analyse the serum markers of liver function and the morphological hepatic changes (by ultrasound) in hypo- and hyperthyroidism.

Methods

The study included 59 patients with hypothyroidism: subclinical disease 14 patients and clinically manifest disease 45 patients, and 30 patients with hyperthyroidism. All patients underwent serum liver function tests: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (Bt), gamma-glutamyl transpeptidase (GGTP), alkaline phosphatase (SAP), and ultrasound monitoring of the liver. The results were compared to those of a control group of 30 patients with the same age and sex parameters.

Results

In hyperthyroidism, increased ALT levels were found in 35.60% of the patients, and nonalcoholic fatty liver disease (NASH) was present in 37.30% of the patients; there was an inversely proportional linear correlation with a high statistical significance between free T4 vs ALT, free T3 vs AST and a directly proportional correlation between TSH vs ALT, TSH vs AST, and TSH vs GGTP. In hyperthyroidism, the prevalence of liver test changes in the patients was as follows: ALT and AST 23.3%, Bt 36.6%, GGTP 36.6%, SAP 53.3%; NASH was common (35%) in those with severe hypothyroidism (TSH > 20.0 mU/l) and 45.0% in clinically overt hypothyroidism (TSH > 50.0 mU/l). The prevalence of NAFLD was estimated to be 22.8% in patients with hypothyroidism and 14.8% in controls. The prevalence of hepatomegaly was lower in hypothyroidism (17.3%) than in controls (21.5%).

Conclusions

It is recommended to monitor the liver function of all patients with thyroid dysfunctions at the time of diagnosis (pre-therapy) and during the evolution of the disease under therapy.

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TPoAAb as an autoimmune response or index of thyroid hypofunction in breast cancer?

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The observed association between thyroid disorders and breast cancer has provoked many investigations. One area where there is some, although far from universal, agreement is the finding of an increased prevalence of anti-thyroid autoantibodies in breast cancer patients compared to controls. Whether this is a feature of a generalised autoimmune response to breast cancer, or provoked by the enzyme thyroid peroxidase acting as an autoantigen, remains unclear. In this study we looked at thyroid antibodies in terms both of their positivity, either detectable or elevated TPOAb. This finding suggests that even the marginally detectable TPOAb levels described in this study may represent more than so-called ‘assay noise’. They indicate, on the basis of serum TSH distribution, that TPOAb positivity may be associated with a subtle thyroid dysfunction which we and others have suggested may be beneficial in terms of breast cancer outcome.

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Brain, mood and cognition during treatment initiation in mild hypothyroidism

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Introduction

Thyroid hormones play an important role in achieving and maintaining reproductive functions. Thyroid dysfunction affects the menstrual cycle and often leads to menstrual irregularity. We prospectively investigated untreated female patients presenting to our Endocrinology and Internal Medicine outpatient clinics.

Material and methods

All the patients were of reproductive age and were newly diagnosed with thyroid dysfunction. After a detailed history (including menstrual history) was taken, TSH, free T3, free T4, anti-Tg, and anti-TPO levels were measured and thyroid ultrasound was performed in all. Thyroid functional status was determined by measurement of TSH, free T4, and free T3. Patients were subdivided into the following groups: overt hypothyroidism (54 patients), subclinical hypothyroidism (106 patients), overt hyperthyroidism (50 patients), subclinical hyperthyroidism (55 patients), and euthyroid patients (Hashimoto’s thyroiditis/modular goiter, 220 patients). Women with normal routine laboratory and imaging studies were classified as controls. Thus, 485 patients and 108 healthy controls were evaluated.

Results

Among patients with overt hypothyroidism, the most frequent menstrual disorders were hypermenorrhoea, menorrhagia, oligomenorrhea, and polymenorrhea. Hypermenorrhoea was significantly more common (33.3%) than in controls (5.6%) (P < 0.05). Among hypothyroid patients, hypermenorrhoea was more common (35%) in those with severe hypothyroidism (TSH > 50.0 mU/l) than in those (16.5%) with mild hypothyroidism (TSH 5–10.0 mU/l) (P < 0.05). The prevalence of menstrual disturbances in the other groups of thyroid dysfunction patients was not significantly different than that of controls.

Conclusion

Thyroid function influences the menstrual cycle and affects reproductive activity, fertility, and pregnancy outcomes. For these reasons, investigation of thyroid function in women with abnormal menstrual activity should be performed.
In the present study, we investigated neural alterations in newly diagnosed patients with mild hypothyroidism due to Hashimoto’s thyroiditis alongside mood and cognition as well as changes with treatment initiation. Animal studies and first studies of human brain metabolism using radioactive tracers suggest neural involvement in affective and cognitive symptoms of hypothyroidism. Here, we introduce non-invasive magnetic resonance imaging (MRI) techniques that allow the analysis of both brain structure and functional connectivity between brain regions and may thus help identifying neural correlates of hypothyroid symptoms. Nine patients and nine healthy matched control subjects (mean age 42.2 ± 8 years; one male each) underwent structural and resting-state functional 3T MRI scanning and comprehensive neuropsychological testing before and 3 months after treatment initiation. Voxel-based-morphometry was used to investigate grey matter density and resting-state functional MRI to analyse the connectivity of brain regions known to be involved in hypothyroidism such as the hippocampus, the amygdala and the anterior cingulate cortex. Treatment restored thyroid hormone levels to the reference range, though the overall effect was small (mean ± s.d. TSH (mU/l): pre 6.1 ± 1.2; post 3.4 ± 1.2). Patients reported significantly higher symptom load, reduced well-being and mental health compared to the control group before but not after treatment initiation. We did not find cognitive impairment or neural alterations even before treatment and no change with treatment. The observed mood alterations could not be related to brain structure or function. The attempt to relate initial treatment effects in mild hypothyroidism to changes in brain structure and function did not produce positive results. Given the small sample size and the mildness of the hypothyroidism, we cannot exclude a false negative finding regarding cognition and brain data. We still want to share the data to avoid publication bias and have thus made them available here for use in meta-analyses: http://neurovault.org/collections/169/. DOI: 10.1530/endoabs.37.EP1049

EP1051
Seaweed derived gaseous iodine: a source of iodine intake in coastal communities?
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This communication tests the hypothesis that iodine (I2) gas or iodine oxides released from seaweeds previously shown to enhance atmospheric iodine adjacent to seaweed hotspots, may through being inspired by respiration, supply a significant fraction of daily iodine requirements. This could assume importance in a country such as Ireland where iodised salt availability is <5%. Iodine intake was assessed by measuring urinary iodine (UI) excretion using a dry ashing technique with Sandell Kolthoff colorimetry. Urine samples were obtained from schoolchildren (n = 167) and adults (n = 481) populations living in coastal areas, including those residing beside a seaweed hot spot, and inland areas of Ireland. Despite dietary iodine intake not varying significantly between inland and coastal communities, the median UI values in the inland areas was 72.5 µg/l (range 58-102 µg/l); coastal areas with limited seaweed growth 70.3 µg/l; seaweed hot spot 145 µg/l. The % of individual readings suggestive of iodine deficiency (<50 µg/l) were greatest in inland areas 27.9 vs 14.3% in limited seaweed growth areas. The lowest proportion of UI values <50 µg/l (3.6%) was observed in the population living beside the seaweed hot spot. Not surprisingly, the greatest number of UI values > 150 µg/l (45.6%) was observed in the seaweed hot spot region. In contrast, relatively few higher UI values (>150 µg/l) occurred in the other regions (range 3.6–11.6%). It is postulated that the most infrequent evidence of iodine deficiency recorded near seaweed hotspots may be the result of atmospheric iodine compensation for inadequate dietary iodine intake through respiration in coastal areas and may assist in maintaining normal thyroid function even when dietary intake is apparently deficient.

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EP1052
Percutaneous ethanol injection as a first line treatment of cystic thyroid nodules: experience after its introduction in a university hospital
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Objectives
To evaluate the efficacy, safety and patient’s pain perception of percutaneous ethanol injection treatment (PEIT) as an alternative to surgery in symptomatic thyroid cysts.

Patients and methods
Thirty consecutive patients (mean age: 46 ± 10 years; 82% women) with symptomatic thyroid cysts relapsed after drainage were included. In all cases, cytology prior to treatment, maximum cyst diameter and volume were determined. PEIT was conducted using the established procedure, and the volume of fluid removed and pain perceived by the patient were assessed. In each procedure, the volume of alcohol instilled was <2 ml. After follow-up, final cyst diameter and volume were determined and the persistence of symptoms was assessed by questionnaire.

Results
Mean symptom duration was 10 ± 20 months. All the cases had a benign cytology. A single session of PEIT was required to complete the procedure in 45% of patients two in 31% and three in 13%. Mean initial maximum cyst diameter was 3.5 ± 1.0 cm and mean extracted liquid volume 61 ± 36 ml. During PEIT, 39% of patients experienced virtually no pain, 43% mild pain and 17% moderate pain. No complications of PEIT were observed. After ≥3 months follow-up, cysts were reduced more than 70% in volume in 86.3% of patients, more than 80% in 61.9% and more than 90% in 42%. Final mean maximum cyst diameter was 1.3 ± 0.6 cm. With respect to cosmetic complaints or local symptoms of compression, PEIT-treated patients presented an initial score of 22 ± 3 and 13 ± 5 at treatment (P < 0.05) and 47% of cases reported a score of 10 (absence of symptoms).

Conclusions
In our experience, percutaneous ethanol injection has proved to be an effective, safe and well-tolerated first-line treatment of symptomatic thyroid cysts.

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**EP1053**

**Soft gel capsule vs liquid thyroxine formulation at breakfast: the results of ‘TITI’ study**

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Levothyroxine (L-T4) is the mainstay of treating hypothyroidism. Despite the ‘classic’ tablet formulation of L-T4, pharmaceutical industries have recently introduced other formulations such as liquid and a soft gel capsule in a few countries. Recent studies have shown a better absorption of these formulations compared with the traditional tablet bypassing the pH-depended dissolution phase and less suffering the binding by sequestrants in the intestinal lumen. Our preliminary data of the ‘TICO’ study, a double-blind, placebo-controlled trial aimed to evaluate the efficacy of oral liquid L-T4 assumed at breakfast, seems to demonstrate that oral liquid thyroxine makes no difference to the thyroid hormonal profile (TSH, fT4 and fT3) regardless assumed before or during breakfast. Based on these preliminary data, we have conducted the 'TITI' (Tirotrin® vs Tiche®, Ibsa farmaceutici Italia) study in order to verify the thyroid hormonal profile of patients assuming L-T4 in soft gel capsule during breakfast. We have enrolled 30 (25/5 female/male, 47.1±11.9 years old) euthyroid patients on stable liquid L-T4 therapy assumed during breakfast. According to the study design all patients switched the liquid formulation to soft gel capsule maintaining the same dosage and the usual breakfast. After 6 weeks TSH, T4 and T3 values were re-tested. At the end of the study no differences to TSH serum (2.61±0.120) and fT3 (2.71±0.269), fT4 (10.43±1.44 vs 9.91±1.25 pg/ml, P=0.120) and fT3 (2.71±0.39 vs 2.83±0.31 pg/ml, P=0.068) were observed among the patients whether assuming liquid or soft gel capsule at breakfast. In conclusion, we have clearly demonstrated that L-T4 soft gel capsule can be taken at breakfast without difference from liquid formulation, facilitating compliance to L-T4 replacement therapy.

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**EP1054**

**The association between sick euthyroid syndrome and hs-CRP in obese patients without comorbidities**

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Inflammation has been shown in obese patients in previous studies. Sick euthyroid syndrome is an expected condition in case of inflammatory diseases. In this study, we aimed to investigate the frequency of sick euthyroid syndrome in obese patients without comorbidities and evaluate the association between obesity and inflammation. A total of 390 subjects were enrolled in this case-control study. The study group consisted of 200 obese patients without comorbidities and the control group consisted of 190 healthy subjects. Thyroid function tests, fasting glucose, insulin, serum lipids, complete blood count, erythrocyte sedimentation rate and hs-CRP levels of all patients were measured. Blood pressures, waist circumference, body mass index were reported. Groups were compared according to the hs-CRP levels and the frequency of sick euthyroid syndrome. The association between hs-CRP and sick euthyroid syndrome was evaluated. The groups were matched in terms of age and sex (P=0.082, 0.186 respectively). There was statistically significant difference among the groups according to the frequency of sick euthyroid syndrome (P<0.001). There was a correlation between the levels of fT4 and hs-CRP in obese patients with sick euthyroid syndrome (P=0.006). In this study, we have found an association between sick euthyroid syndrome and obesity. Moreover, we have found a correlation between sick euthyroid syndrome and hs-CRP level. These results showed that obesity (without any comorbidities) is an inflammatory disease and has systemic effects which lead to sick euthyroid syndrome.

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**EP1055**

**Efficacy and safety of radiofrequency ablation performed by an endocrinologist for large benign thyroid nodules**

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Background
Radiofrequency ablation has recently been used for the treatment of benign thyroid nodules, with outstanding results. However, in most related studies, smaller nodules (<2 cm) were included and the procedure was usually performed by a radiologist or surgeon. Therefore, this study evaluated the efficacy and safety of radiofrequency ablation for nodules >2 cm performed by an endocrinologist with several years of experience performing fine-needle aspiration cytology.

Methods
This study was a cross-sectional analysis of 111 patients who received radiofrequency ablation between April 2010 and July 2013: 73 patients with 75 nodules >2 cm in diameter with at least 6 months of follow-up examinations were included.

Results
The mean follow-up period was 11.5 months. The mean nodule volume decreased from 17.0±15. ml preoperatively to 6.0±8.5 ml postoperatively, with a mean volume reduction of 69.7%. There were no major complications, and only one patient (1.3%) presented with a minor complication (haemorrhaging of the thyroid parenchyma).

Conclusions
Radiofrequency ablation is a safe method for reducing the size of large benign thyroid nodules and is not associated with any major complications.

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**EP1056**

**Prediction of the size of benign thyroid nodules and an analysis of associated factors**

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Background
Most thyroid nodules are benign therefore, they are commonly only monitored. Only a few studies are available on the natural progression/regression of benign thyroid nodules, and large-scale studies on the subject are non-existent. So we identify factors that affect the size of benign thyroid nodules and to predict the potential nodule size through a model.

Methods
Between January 2001 and December 2011, 2,469 benign thyroid nodules (1,564 patients) were diagnosed through fine needle aspiration. After excluding 505 nodules for which either the volume was unknown or percutaneous ethanol injection or radiofrequency ablation had been performed, 1,964 benign thyroid nodules (1,261 patients) were selected for the retrospective analysis in our study.

Results
The nodules with increased size over time involved a longer follow-up period than the nodules with decreased size. The proportions of females and cystic portion were relatively high. For the thyroid nodules with increased size, we analysed the potential influencing factors. Our analysis results indicate that larger nodule volume, extended follow-up period, and high cystic proportion were all positively associated with increased nodule size.

Conclusion
Controlling for all other potential variables, the thyroid nodules tended to grow at a rate of approximately 0.034 cm² per year in the group with continually growing nodules. The model used in our study may offer helpful insight in determining an optimal treatment schedule for benign thyroid nodules.

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**EP1057**

**Investigation of GLP-1 and GIP levels change in patients with hyperthyroidism before and after treatment**

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The main hormones responsible for the incretin effect are GIP and GLP-1. Thyroid hormones accelerate the absorption of glucose from the intestine, increase the release of glucose from glycogen stores and affect the hepatic...
Several levo-thyroxine (L-T4) formulations are now available. However, scientific societies discourage the use of generic L-T4 owing to its uncertain bioavailability in comparison with brand L-T4. Recent literature data suggest that using a liquid formulation of brand L-T4 improves the management of hypothyroidism. However, it is not clear whether patient satisfaction improves on liquid (LI) L-T4 as patients may initially be reluctant to switch from their tablet (TA) formulation to a ‘new’ (LI) L-T4. The aim of this study was to evaluate efficacy, tolerability and quality of life (QoL) changes in Hashimoto’s thyroiditis patients who began de novo L-T4 treatment for sub-clinical or overt hypothyroidism. Patients were randomized to LI (n = 15) or TA (n = 16) L-T4 formulation (IBSA Farmaceutici). After 6 months, they switched from one formulation to the other. Clinical and hormonal data were collected at the baseline and after 1st titration, 6 (crossover), 7 (2nd titration) and 12 (end of study) months. Hypothyroid symptoms were scored on the Billewicz scale (BS); subjective satisfaction and QoL were evaluated by means of a visual analogic scale (VAS) and the ThyPRO inventory. On randomization, sex distribution (85% females), median age (59 years), thyroid volume (8 ml), blood pressure (systolic 120 mmHg; diastolic 80 mmHg) heart rate (70 bpm) and concomitant therapies (1 drug on average), but not BMI (TA 26.7±1.3 kg/m²; LI 22.7±0.8 kg/m²; P = 0.02), were similar between groups. BS scores (LI 3.8±0.4; TA 2.7±0.4; P = 0.06), TA1, TA2 (LI 1.7±0.7; 0.7±0.7 mg/dl; TA 9.1±1.6; P = 0.1) and TSH (LI 21.5±8.4 IU/l; TA 11.0±2.5 IU/l) were not statistically different. ThyPRO scores did not differ between groups at the baseline. In both groups, L-T4 treatment was begun at a dosage of 50 μg/day. Before the 1st titration, seven women (LI 27% TA 19%) withdrew their consent and dropped out. After titration, the dosages were similar in both groups (LI 46.1±4.1 μg/kg per day; TA 55.8±3.0 μg/kg per day). On crossover, clinical data remained unchanged. BMI was slightly lower at 6 months (P = 0.003) in LI (23.6±0.9 kg/m²) than in TA (26.0±1.2 kg/m²) subjects. On LI-T4 treatment, BS scores decreased in both groups (LI 2.4±0.4; TA 1.3±0.4; P = 0.1). No differences were noted between groups in terms of VAS (LI 8.4±2.0, TA 8.1±0.4) or laboratory data. A reduction on all ThyPRO scales was noted in both groups. To improve median TSH levels (LI 3.6 mIU/l; TA 3.3 mIU/l) after crossover and 2nd titration, LI-T4 dosages were increased in 43% and 29% of patients on LI and TA-LT4, respectively. Intention-to-treat analysis revealed similar median BS (LI 3, TA 2.0) and VAS (LI 8, TA 7.5) scores and median TSH (LI 3.6 mIU/l; TA 6.0 mIU/l) levels at the end of the study. After 12 months of L-T4 treatment, 60% of subjects required a further increase in LI-T4 dosage, in both formulations, to adequately control hypothyroidism. At the end of the study, only the ThyPRO scales ‘eyes’, ‘anxiety’ and ‘cosmetic complaints’ had improved less on LI than on TA therapy. In conclusion, LI-T4 was better tolerated by a high number of drop-outs; the number of data available may therefore constitute a limitation to the study. Both LI and TA L-T4 formulations displayed similar efficacy. However, dosages need to be carefully increased when treatment for control of hypothyroidism is started de novo. The tolerability of LI and TA-T4 proved similar and QoL improved in all patients on therapy.

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**EP1059**

**Serum Galectins are increased in patients with Graves’ disease hyperthyroidism**

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Introduction

Patients with autoimmune thyroid disease (AITD) exhibit aberrant immune-regulatory mechanisms. Galectins (Gal) are a family of glycan-binding proteins, which have been involved in immune regulation. However, the association of Gal with AITD remains unknown. In this study, we evaluated serum Gal and 11D in patients with AITD.

Methods

Peripheral blood samples from 31 patients with Graves’ disease (GD) (14 with untreated hyperthyroidism, nine euthyroid with treatment, eight with iatrogenic hyperthyroidism), 26 Hashimoto’s thyroiditis (HT) (20 hypothyroid, six euthyroid with treatment), 12 non-GD hyperthyroid patients (NG) and 24 healthy controls were studied. Serum levels of thyroid hormones, thyroid antibodies (Ab), Gal-1 and Gal-9 were measured on the same day (FT4 by RIA; TSH, Tg-Ab, TPO-Ab and TSHR-Ab by immunoradiometric assays; Gal-1 and Gal-9 by ELISA).

Results

Serum Gal-1 (ng/ml) and Gal-9 (pg/ml) were significantly increased in GD (3.756 and 8.582 respectively), HT (3.085 and 9.188) and NG (2.822 and 8.983), in comparison to controls (1.508, 7.323), P < 0.005. No significant differences in Gal levels were found between the first three groups. Patients with hyperthyroidism (both GD and NG) had higher Gal-9 levels than euthyroid AITD patients, although there were no differences in Gal-1. In fact, in GD, we observed a direct correlation between Gal-9 and FT4 (r = 0.41, P = 0.004), and an inverse correlation between Gal-9 and TSH (r = 0.47, P = 0.01). We did not find an association between Gal-9 and Ab levels in either group of AITD, although an association between Gal-1 and TPO-Ab levels was found in HT (r = 0.512, P = 0.005). Antithyroid treatment reduced Gal-1 levels in patients with GD.

Conclusions

Galectins may be involved in the severity and pathogenesis of AITD, and could potentially be used as a diagnostic and therapeutic marker.

Disclosure

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**EP1060**

**Paraoxonase and arylesterase levels in autoimmune thyroid diseases**

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Objective

The aim of this study was to evaluate paraoxonase-1 (PON1) activities and its association with oxidative stress status in autoimmune thyroid disease (AITD).

Materials and methods

Patients with 25 Hashimoto thyroiditis (HT) and 25 Graves’ disease (GD) and 27 healthy controls were enrolled in the study. Blood samples were obtained in euthyroid period and 3 months after the initiation of medical treatment. Serum samples from AIT diseases and healthy control group were analysed for paraoxonase (PON), arylesterase (ARE) activities, lipid hydroperoxide (LOOH) and total free sulfhydryl (–SH) levels.

Results

The preoperative PON and –SH levels of the patients with AITD were significantly lower compared to those of the control group (P < 0.001, for each), while LOOH levels were significantly higher (P < 0.001, for each). There was no significant difference between the patients with AITD and the healthy control groups in terms of ARE levels (P > 0.05). PON levels showed a positive correlation with –SH (r = 0.522, P < 0.001) and a negative correlation with LOOH (r = 0.487, P < 0.001).

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EP1061
Reference values of TSH, FT4 and FT3 in a cohort of pregnant women in the north of Spain

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Introduction
As soon as pregnancy is established, various physiological changes occur in maternal thyroid economy. Due to that, the reference limits of thyroid parameters used for the general population are no longer valid to diagnosis thyroid dysfunction during pregnancy.

Methods
We included 266 pregnant women, with no thyroid disorders and resident in Cantabria, a region in northern Spain. They were questioned about iodized salt and iodine supplements intake and blood samples for TSH, FT4, and FT3 were obtained in the first and third trimester of gestation and for TPO abs and Tg abs in the first trimester.

Results
Eighteen patients (6.76%) were TPO abs or Tg abs positive. Iodized salt was consumed by 39.8% in the first trimester and by 83.5% in the third (P < 0.001 and iodine supplement by 70.7% in the first and 91.2% in the third (P < 0.001). Reference values, expressed as median and 2.5 and 97.5 percentiles were: TSH 1.67 μIU/ml (0.27-4.16), FT4 1.06 ng/dl (0.86-1.31), FT3 2.97 pg/ml (2.42-3.65) in the first trimester and TSH 1.92 μIU/ml (0.57-4.01), FT4 0.89 ng/dl (0.70-1.08), FT3 2.85 pg/ml (2.24-3.51) in the third trimester. If we exclude TPO abs or Tg abs positive women from the analysis, reference values were: TSH 1.63 μIU/ml (0.27-4.13), FT4 1.06 ng/dl (0.86-1.31), FT3 2.97 pg/ml (2.42-3.64) in the first trimester and TSH 1.92 μIU/ml (0.65-3.95), FT4 0.88 ng/dl (0.7-1.07), FT3 2.85 pg/ml (2.27-3.53) in the third trimester. Difference between the first and third trimester were significant for TSH, FT4, and FT3 in both groups. The small group of women with positive TPO abs or Tg abs, presented a higher TSH in the first trimester compared with women without antibodies.

Conclusion
Serum PON levels is decrease in patients with AIT, and serum PON is positively correlated with –SH, a well known antioxidant, and negatively correlated with LOOH, an oxidant.

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EP1063
The effect of vitamin D on thyroid autoimmunity
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Introduction
Although, vitamin D (vit D) mainly regulates calcium and phosphate metabolisms, its deficiency may also contribute to the development of some carcinomas, autoimmune, and cardiac diseases. Vit D deficiency has been defined to correlate with increased autoimmune disease such as type 1 diabetes mellitus, rheumatoid arthritis, autoimmune thyroid diseases (AITD). Previous studies suggested that patients with AITD had lower vit D levels when compared with healthy controls. Moreover, vit D supplements were found to prevent the development and progression of autoimmune disorders such as type 1 diabetes mellitus and multiple sclerosis. Thus, we aimed to assess the effect of vit D on thyroid antibody titers in patients with AITD.

Methods and materials
Twenty-four participants were enrolled into the study. All of the participants were diagnosed with AITD and vit D deficiency. We assayed the serum anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg) antibody levels before and a month after the vit D replacement. The daily dose of the vit D replacement was 2000 International Units (IU).

Results
The AITD induced disorders in participants were as following: subclinical hyperthyroidism: 66.6%, subclinical hypothyroidism: 8.3%, overt hyperthyroidism: 12.5%, and overt hyperthyroidism: 12.5%. Mean vit D level was 13.1 ± 12.2 nmol/l. Before and after vit D replacement, anti-TPO titer was 276.6 ± 42.7 IU/ml, 257.1 ± 40.1 IU/ml (P < 0.001), and anti-Tg titers were 371.9 ± 64.3 IU/ml, 269.3 ± 36.4 IU/ml (P < 0.001) respectively. There was a statistically significant decrease in the anti-TPO and anti-Tg levels after the vit D replacement.

Conclusion
Vit D supplements seem to reduce thyroid antibody titers which play the main roles in the development and progression of AITDs. Therefore, vit D therapy may be used in the treatment of patients with AITD, particularly those with vit D deficiency.

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EP1064
Endocrine involvement in systemic amyloidosis.
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Introduction
Systemic amyloidosis leads to functional compromise of various organs through infiltration of these tissues by amyloid protein.
The aim of this study was to determine the endocrine disorders in patients with systemic amyloidosis.

Methods
During the period from 1975 to 2006, we collected 580 patients with renal amyloidosis confirmed by histological exam. We selected 123 patients with hormonal examination. 55 patients had thyroid function tests and 68 patients had adrenal function tests.

Results
There were 85 males and 38 females with an mean age of 49.6±18 years. Seventeen patients had primary hypothyroidism (30.9%) and ten patients had primary adrenal insufficiency (14.7%). The diagnosis of hypopituitarism was established in 18 patients with a central hypothyroidism in 14 cases and an adrenocorticotrophic hormone deficiency in four cases. None of the patients had a simultaneous achievement of two pituitary abnormalities but one patient had TSH deficiency associated with adrenal insufficiency. Goiter was observed in nine patients with hypothyroidism in four cases.

All patients with adrenal insufficiency, ten patients with low TSH and five cases of goiter had AA amyloidosis.

Conclusion
Endocrine disorders such as hypothyroidism and adrenal deficiency were frequent in renal amyloidosis. Therefore their screening is necessary for an early treatment to improve patient’s prognosis.

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EP1065
Amyloid goitre as the first manifestation of systemic amyloidosis
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Introduction
Thyroid gland may be asymptptomatically involved in most patients with secondary systemic amyloidosis. However, clinically detectable amyloid goiter is quite rare: often it is seen in patient with kidney involvement. We report one case of amyloid goiter without kidney manifestation.

Case report
A 30-year-old male diagnosed with bilateral bronchiectasis since 1992 was admitted with rapidly growing goiter associated with dysphagia for solids, change in voice, weight loss and dyspnea. The goiter was nodular large and hard. The rest of the examination was normal. His thyroid function tests were normal, antithyroglobulin and antimicrosomial antibodies were negatives. As he had signs of compression, total thyroidectomy was performed without complication. Histological exam showed type AA amyloid throughout the gland. Labial biopsy was positive for type AA amyloid. Evolution was favorable and 2 years later proteinuria was still negative.

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Conclusion
We report perhaps, a new case of amyloid goiter without renal manifestation in the course of secondary amyloidosis. A preoperative diagnosis of amyloid goiter must be considered in patients with thyromegaly who have a predisposing risk factor for developing amyloidosis.

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EP1066
A questionnaire on quality of life identifies Graves’ ophthalmopathy patients who deserve more attention
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Introduction
Graves’ ophthalmopathy (GO) varies from minor changes to visible face disfigurement which may compromise the visual capacity and the aesthetics of the patient. These deformities affect the quality of life in both functional and emotional senses. There are some questionnaires designed to evaluate the patient’s health, quality of life and relationship with a specific disease. The use of these questionnaires is recommended to improve the quality of care and, mainly, to identify patients who are in need of psychological support. However, they need to be validated in each country.

Methods
We evaluated 140 consecutive Brazilian GD patients investigating the severity of their ophthalmopathy (Clinical Activity Score), and quality of life, according to the questionnaire on quality of life in Graves’ ophthalmopathy (GO-QoL).

Results
The patients were divided in two groups according their initial CAS. Group 1 (CAS 0 or 1), n=108, and group 2 (CAS ≥ 2), n=32. There were no differences in age, duration of disease and gender between the groups. However, group 1 had better results concerning the score of total visual functioning (P<0.005) and the score of total appearance (P<0.001); patients in group 2 were more affected on simple tasks such as moving around the house (P<0.05), walking outdoors (P<0.005), reading (P<0.05), watching TV (P<0.005). In addition, this group had a worse score on self-confidence (P<0.001) and felt hindered from doing something they wanted to do because of GO (P<0.05).

Conclusion
GO significantly affects the quality of life and the use of the GO-QoL questionnaire permitted to identify patients who deserve specific attention.

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EP1067
Abstract withdrawn.

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EP1068
Graves’ disease and HIV infection: bad response to antithyroid drugs due to interaction with HIV therapy
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Graves’ disease and HIV infection: bad response to antithyroid drugs due to interaction with HIV therapy
Graves' disease is one of the multiple autoimmune diseases that have been reported in HIV-infected patients. With the upsurge of highly active anti-retroviral therapy (HAART) the incidence of autoimmune diseases in HIV-infected patients is increasing, especially after immune reconstitution. We present a male, 51-year-old, who started complaining with anxiety, suderosis and palpitations. The laboratory workout revealed hyperthyroidism: TSH <0.02 µU/ml (0.46-4.68), FT4 28 pmol/l (10.0-28.2), FT3 13.7 pmol/l (4.26-8.10). The patient started propylthiouracilo 100 mg per day and was referred to the Endocrinology Department. He had Mitral Insufficiency and HIV-1 infection. He was on HAART since 2007 with emtricitabin, tenofovir, atazanavir and ritonavir. The etiologic study disclosed Graves disease with TRAbs level 45.3 UI/l (<1). We changed propylthiouracilo for thiamazole. During follow-up most of the time it wasn't possible to achieve euthyroidism. We offered other therapeutic options (iodine-131 or surgery) but the patient rejected them. On the 23rd month of thiamazole therapy the patient was icteric and blood workout revealed hyperbilirubinemia (total bilirubin 8.1 mg/dl), FT4 48.1 pmol/l and FT3 18.7 pmol/l. We discussed these results with the Infectiology Department and hyperbilirubinemia was interpreted as an atanavir adverse effect. Boosted atazanavir (with ritonavir) was replaced by rilpivirine and we maintained the same dosis of thiamazole (15 mg per day). 6 weeks later he had normal total bilirubin (0.64 mg/dl) and normal/low thyroid hormones: FT4 9.45 pmol/l and FT3 6.05 pmol/l. Both atazanavir, ritonavir and thiamazole are metabolized in cytochrome P450. In this case the interaction resulted in decreased benefit of thiamazole and explains why it was so difficult to attained euthyroidism. To the best of our knowledge this is the first time the interaction between atazanavir and thiamazole is reported.

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EP1069

Abstract withdrawn.

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EP1070

Plasma visfatin/pre-B-cell colony enhancing factor levels in hypothyroid patients and relationship of these levels with thyroid autoimmunity and atherosclerosis

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Visfatin/pre-B-cell enhancement factor is an adipocytokine, which is found in the visceral fat tissue and enhances the growth of precursor of B cells through showing synergy with IL-7 and stem cell factors. Other cytokines released from the adipose tissue are TNFα and IL-6, which has been shown to be related with pathogenesis of insulin resistance, diabetes, dyslipidaemia, inflammation, and atherosclerosis. Our aim was to determine the relationship of plasma visfatin/pre-B-cell colony enhancing factor levels with thyroid autoimmunity and atherosclerosis. The study was performed randomly on 35 patients (32 women/three men, mean age 43.8 ± 9.6 years) diagnosed with Hashimoto's thyroiditis and 18 healthy controls (17 women/one men, mean age 43.3 ± 5.2 years) attending our outpatient clinic between June 2009 and January 2010. Before therapy anthropometric levels, carotid intima-media thickness (CIMT), serum anti TG, anti TPO, hsCRP, homocystein, lipop(a), ApoA, ApoB1, β-2 microglobulin, insulin, glucose, visfatin, IL6, TNFα, oxidized-LDL levels, and lipid profile was measured. Plasma visfatin oxidised LDL, IL6, and TNFα levels did not differ from the control group before and after therapy in hypothyroid patients, statistically. The cardiovascular risk factors like systolic and diastolic blood pressure, HOMA-IR index, triglyceride, Apo B and ApoB/ApoA, homocystein, β-2 microglobulin, and CIMT were found to be elevated in the patients. Ox-LDL, cholesterol, homocysteine, and proteinuria levels were positively correlated with anti-Tg levels. Conclusionally, we think that non-traditional CVD risk factors are elevated in hypothyroid Hashimoto’s thyroiditis patients and as a atherosclerosis indicator CIMT increase accompanies it and anti-Tg antibody is a bridge between autoimmunity and atherosclerosis.

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EP1071

Could thyroid replacement therapy not be enough to reduce oxidative stress in hypothyroid patients with Down’s syndrome? A cohort study

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Hypothyroidism and autoimmune thyroiditis are common in patients with Down’s syndrome (DS), leading to common prescription of thyroid replacement therapy. On the other hand, thyroid function is involved in oxidative stress (OS) mechanisms. DS is a well-known high OS condition because several genes involved in OS mechanisms map on chromosome 21 and coenzyme Q10, lipophilic antioxidant, could be more correlated with hypothyroidism than TSH in DS people. To investigate relationships among thyroid function, OS and replacement therapy, we enrolled 26 adults with DS (ten males) aged 18–64. Fourteen were under thyroid replacement therapy with levothyroxine. A fasting blood plasma was collected at 0900 h and TSH (NR 0.30–2.80 µU/ml), fT4 levels and total antioxidant capacity (TAC) were evaluated.

TAC was evaluated with colorimetric method, using the system metamyoglobin-H2O2, and the chromogen ABTS; the latency time (LAG, s) in the appearance of ABTS radical proportional to antioxidant content of the system. Patients were classified in two groups: i) patients under thyroid replacement therapy (14/26) and ii) patients without replacement therapy (12/26). Among the first group, 57% (8/14) of patients were euthyroid (mean ± s.d. TSH 3.01 ± 3.27), whilst 42% (5/12) were hypothyroid in the second group (mean TSH 2.59 ± 1.09). TAC was lower in the first group (62.50 ± 14.64) than in the second group (74.17 ± 12.40), regardless of TSH level. These data confirm hypothyroidism as a high OS condition and suggest that replacement therapy alone could not be enough to establish normal TAC levels in hypothyroid patients. Further studies will be necessary to evaluate whether a supplementation with antioxidants should be considered in DS hypothyroid patients, due to the competence of two causes of high oxidative stress in those patients. It could also be necessary to evaluate whether non-DS hypothyroid patients under thyroid replacement therapy show higher OS levels.

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EP1072

Hypothyroidism and the haemodialysis patients: it is a matter for discussion

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149 haemodialysis chronic renal failure (CRF) patients on haemodialysis (HD) program of 4/6three times a week investigated for thyroid gland function and try to answer the question: is the thyroid function abnormality affect the response of the haemodialysis CRF patients to recombinant human erythropoetin (rHuEPO)? We compare the results of the thyroid gland markers: T3, T4 and TSH (which tested by minividas technique) of the patients with the packet cell volume (PCV) values of the patients and showed if the haemodialysis CRF with hyper or hypothyroidism affect the response of the patients to the rHuEPO and if there are differences in the values of the PCV between the groups of the patients after fixed the duration and the times of the HD session and the same dose and route of the rHuEPO. The results analysed statistically and discussed and from that we can concluded there are hyporesponsiveness of the rHuEPO in patients with CRF and hypothyroidism in haemodialysis and for this reason we advise to search any haemodialysis patients for thyroid function.

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EP1073

The changes of thyroid function after coronary angiography in Koreans with normal hypothyroidism at 12 weeks after CAG with PCI.

There were no changes of thyroid function after CAG in Koreans with normal hypothyroidism at 12 weeks after CAG with PCI. Among the three patients, one patient remained subclinical patients were newly diagnosed as subclinical hypothyroidism at 1 week after PCI. The total cholesterol level also showed a positive correlation with patients’ concerns of cold intolerance (R = 0.3, P = 0.001), hair problems (R = 0.28, P = 0.003), feeling sick (R = 0.2, P = 0.02), and neuropathic pain (R = 0.3, P = 0.04). Conclusion We cannot rely on the TSH level alone as a marker of optimal treatment outcome in patients with primary hypothyroidism because it does not reflect the concern status of the patients.

EP1074

Clinical and social concerns in treated patients with primary hypothyroidism in Basra:

A cross sectional study

Background Despite available treatment for hypothyroidism, levothyroxine replacement therapy in a biochemically appropriate dose does not necessarily relieve patients' symptoms and complaints. The aim of the study was to evaluate the concerns of patients treated with hypothyroidism and to correlate these concerns with different patient characteristics and thyroid biochemical control.

Method

One hundred and eighteen treated primary hypothyroid patients attending Al-Faiha Diabetes Endocrine and Metabolism Center (FDEMC) in Al-Basrah were entered into a questionnaire designed to capture personal, anthropometric, biochemical, and clinical data. Twenty-four concerns were questioned to the patients who score these concerns on a four point Likert scale.

Results The most scored patients’ concerns were fatigue, neuropathic pain, lack of weight loss, cold intolerance, breathing problems, and swallowing problems. No statistically significant relations were existed between these concerns and TSH control, except for a high TSH group which were highly likely to have concerns of feeling sick (OR: 0.27, 95% CI 0.54–2.0, P = 0.001), neuropathic pain (OR: 0.4, 95% CI 0.17–1.6, P = 0.01), cold intolerance (OR: 0.35, 95% CI 0.3–1.7, P = 0.005), and hair problems (OR: 0.26, 95% CI 0.6–2.1, P = 0.001). While they were less likely to have concerns about lack of weight loss (OR: 8.7, 95% CI –2.9 to –1.3, P < 0.0001) and permanent medication (OR: 2.7, 95% CI 1.8 to 3.5, P = 0.003) than in normal TSH patients where these concerns scored more and significantly. A significant correlation existed between duration of the hypothyroidism and patients’ concerns of swelling of the hands and feet (R = 0.7, P < 0.0001), memory problems (R = 0.4, P < 0.0001), hearing disturbance (R = 0.38, P < 0.0001), and hair problems (R = 0.3, P = 0.001). Figure significantly affects patients concerns of memory problems (R = 0.6, P < 0.0001), swelling of the hands and feet (R = 0.4, P < 0.0001), and hearing disturbance (R = 0.37, P < 0.0001). Positive correlation was present between LDL cholesterol level and patients’ concerns of cold intolerance (R = 0.3, P = 0.001), hair problems (R = 0.28, P = 0.003), feeling sick (R = 0.2, P = 0.02), and neuropathic pain (R = 0.3, P = 0.04). The total cholesterol level also showed a positive correlation with patients’ concerns of cold intolerance (R = 0.3, P = 0.001), hair problems (R = 0.25, P = 0.01), neuropathic pain (R = 0.22, P = 0.01), and fatigue (R = 0.2, P = 0.04).

Conclusion

We cannot rely on the TSH level alone as a marker of optimal treatment outcome in patients with primary hypothyroidism because it does not reflect the concern status of the patients.

EP1075

Ultrasonographical and cytological features of exophytic thyroid nodules: do exophytic nodules pretend to be malignant?

Exophytic nodule refers to a nodule that sticks out of the normal thyroid boundary/outline. Different definition is a nodule with an acute angle between the lesion and adjacent thyroid capsule. In the literature, one study reported thyroid nodules with exophytic configuration showed a high malignancy rate. We aimed to compare ultrasonographical features and cytopathologic results of exophytic and non-exophytic thyroid nodules.

Material and method

Thirty-four exophytic and 34 non-exophytic thyroid nodules in which fine-needle aspiration biopsy was indicated throughout 3 months were evaluated prospectively. Mean nodule size was similar in two groups (18.83 ± 8.71 and 15.28 ± 7.57 mm, P = 0.173). The ratio of presence of peripheral hypoechoic halo and marginal irregularity was also similar in both group (P = 0.512 and P = 0.153 respectively). Microcalcification was present in 21.4 and 29.4% of exophytic and non-exophytic nodules respectively (P = 0.424). Macrocalcification was detected in 4.5% of exophytic and 11.8% of non-exophytic nodules (P = 0.111). 47.6% of exophytic nodules was hypothyroid and 32.4% was euthyroid. 47.1% of non-exophytic nodules was hypothyroid and 52.9% was euthyroid. Flow Doppler pattern was defined as non-vascular, peripheral, central, or of mixed type and was similar in both groups (P = 0.138). Cytopathologic results of exophytic nodules were 75% benign, 4.3% follicular lesion or atypia with undetermined significance, 2.3% suspicious for malignancy, 2.3% malign, and 19.5% non-diagnostic. In non-exophytic group, 79.4% was benign and 20.6% was non-diagnostic (P = 0.497).

Conclusion

Exophytic configuration of thyroid nodules was rarely investigated as a possible predictive feature for malignancy in the literature. In this study, we did not find any difference in terms of ultrasonographical features and cytological results between exophytic and non-exophytic thyroid nodules. However, more comprehensive studies are needed to clarify any possible relation between exophytic configuration and malignancy.
Fine-needle aspiration biopsies (FNAB), adequate for examination, reported as benign re-evaluated with histopathological samples. 61 patients, females and nine males re-evaluated. 41 of them reported as benign. 20 of the patients, seven females and three males reported as papillary carcinoma. Six of the papillary carcinomas were single focus, two multicentric, and 12 papillary microcarcinoma. Six of the eight patients malignant lobe was different from the lobe that FNA was made. Multicentric malignancy was detected in two cases. Malignant FNA diagnosis forms 4–8% of all thyroid FNAs, as in literature. Most of them are papillary thyroid carcinoma (PTC). In fact PTC cytological features are quite obvious, at the level of diagnostic. Patients diagnosed PTC with FNAB showed PTC at the rate of 96–100% with histopathological samples. However, false-negative value was 32.78% in our patients under observation. This value is over the false-negative rate ranging between 1.22 and 21.3% stated in the literature. However, the results of the histopathological report with the results of cytopathological reports examined in detail the majority of the cases with false-negative study (60%) constitute papillary microcarcinoma. This finding suggests that PTC is overlooked with FNAB. Our false-negative rates are compatible with the literature as PTC excluded. Another reason for our false-negative value is the patchy distribution of PTC in the single nodule. As a result, FNAB accompanied with ultrasound, should be applied to all solid, hypoechoic nodules and nodules with microcalcification. Also, because of the presence of PTC showing a patchy distribution in a single nodule, multiple biopsies should be taken from more than one areas, from the large nodules seen sonographically suspicious.

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EP1079

Multiple disease associations in autoimmune polyglandular syndromes

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Introduction

Autoimmune polyglandular syndromes (APS) are a heterogeneous group of disorders characterised by autoimmune activity against endocrine and non-endocrine organs. APS type depends on the combination of the diseases (APS1, APS2, APS3).

Methods

The study was conducted in 89 patients (70F and 19M) with APS aged mean 50.00±14.80 years, treated at Endocrinology Department between 2003 and 2015. We analysed clinical manifestations, results of laboratory tests and imaging to determine the components of APS.

Results

The most common syndrome was APS3 (69.66%). 24.72% of patients had APS2, only five subjects (5.62%) suffered from APS1. Autoimmune thyroid disease was found in 84.27% of cases, i.e. Hashimoto’s thyroiditis (58.43%) and Graves’s disease (25.84%), and in 100, 86.36, and 82.26% of APS1, APS2, and APS3 cases respectively. Type 1 diabetes had been diagnosed in 61.80% of participants (in 20.00, 27.27, and 77.42% of APS1, APS2, and APS3 cases respectively). Besides patients with APS2, all subjects with APS1 were treated due to Addison’s disease which was found in 29.21% of APS patients. Other problems such as: vitiligo (17.98%), psoriasis (12.36%), Addison-Biermer anemia (10.12%), alopecia areata (5.62%), asthma (3.37%) and in individuals – rheumatoid arthritis, myasthenia gravis, coeliac disease, ulcerative colitis, and autoimmune hepatitis were observed. In APS1, three to six diseases were noted, mostly the coexistence of Addison’s disease and hypoparathyroidism. Two to three diseases were found in APS2. Schmidt’s syndrome was determined in 63.64% of patients with APS2, Carpenter syndrome only in two cases. The most common diseases in APS2 were: Hashimoto’s disease, type 1 diabetes, Graves’s disease (72.73, 27.27, and 13.64% respectively). In APS3, two to four diseases were found. Type 1 diabetes, Hashimoto’s disease, and Graves’ disease were the most common disorders (77.42, 50.00, and 32.26% respectively). The most common coexistence in APS3 was type 1 diabetes with Hashimoto’s disease.

Conclusions

Although, some diseases occur more frequently than others, it should be remembered about various APS components during follow-up such patients.

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**EP1080**

Intraocular pressure, corneal, and retinal thickness in patients with euthyroid autoimmune thyroiditis


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Introduction

Ocular changes and ocular symptoms may be encountered in patients with hypothyroidism and hyperthyroidism. However, the data concerning the effects of thyroid disorders on intraocular pressure (IOP), central corneal thickness (CCT), and retinal thickness (RT) are very rare. Here, we aimed to evaluate the alterations in IOP, CCT, and RT in patients with euthyroid autoimmune thyroiditis (AIT).

Methods

Twenty-five subjects with euthyroid AIT were included into the study. The patients were compared with age and sex-matched 40 healthy subjects. A detailed ophthalmologic examination including the IOP, CCT, and RT was performed in both groups.

Results

There was not statistically significant difference in mean right RT, left RT, right CCT, and left CCT between two groups (P>0.05 for all parameters). Also, no significant difference was found between groups concerning right and left IOP (P>0.05 for all parameters). In patients groups, left RT was significantly higher in patient with TSH > 2.5 μIU/ml than those of TSH < 2.5 μIU/ml (294.85±23.58 μm vs 261.50±21.70 μm, P = 0.003). A positive correlation was observed between left RT and TSH levels (r = 0.269, P = 0.033). No significant correlation was found between free triiodothyronine levels, and right CCT, right RT, right IOP, left CCT, left RT, and left IOP levels (P>0.05 for all parameters). Also, free tetraiodothyronine levels were not significantly correlated with right CCT, right RT, right IOP, left CCT, left RT, and left IOP levels (P>0.05 for all parameters).

Conclusion

An increase in IOP in Graves’ ophthalmopathy is a well-known entity. In literature, hyperthyroidism seems to cause a reversible increase in CCT and IOP. In this study, we observed no significant difference between groups concerning IOP, CCT, and RT. So, further studies with larger sample size are needed to evaluate IOP, CCT, and RT in patients with euthyroid AIT.

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**EP1081**

Should fine-needle aspiration biopsy perform all of nodules in patients with nodular goitre?


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Introduction and aim

Fine-needle aspiration (FNA) biopsy has become widely accepted as a reliable method for diagnosis of malignant thyroid nodule. In our study we aimed to review results of thyroid FNA biopsy to be performed by same endocrinologist and compared to their histopathological results after thyroidectomy.

Materials and methods

This retrospective study was done at the department of pathology for a period of 2 years from 2012 to 2014. The 401 patients applied to our Endocrinology Department due to solitary or multinodular goitre was included the study. Ultrasonography guide was used in all of FNA. FNA findings according to Bethesda classification were compared with corresponding histopathology findings, obtained with thyroidectomy specimens.

Results

After thyroidectomy, we determined that eight women (mean age 50.7±6.8 years) of 401 patients with nodular goitre had papillary thyroid cancer in a cross thyroidal lob which FNA was not made, although finding of FNA was benign at one thyroid lob which FNA was made. Moreover, multicentric papillary thyroid cancer was found in two of them after thyroidectomy.

Conclusions

Our landmark finding point out that FNA should be performed all of suspicious nodule rather than dominant nodule. On the other hand multicentric papillary thyroid cancer are still a problem, although, FNA is widely used for evaluate cytology of nodules.

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**EP1082**

Hyperthyroidism in Internal Medicine Services in Spain (2005–2012)


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Introduction

The prevalence of hyperthyroidism in patients admitted in Internal Medicine at Spanish hospitals is 0.8%. Proper diagnosis and management of these patients is still a challenge and therefore, the analyses of the factors involved in the prognosis and survival is of interest.

Methods

Data from the minimum-data-set (MDS) of Spanish National health System were collected during 2005–2012 from discharged patients of Internal Medicine with HTD diagnosis. A bivariate analysis was performed in order to detect differences in the mortality rate, median age, median hospital stay, readmission rate and comorbidities among HTD and non HTD (NHTD) patients. A logistic regression analysis was performed using as dependent variable in-hospital mortality and sex, mean age, adjusted comorbidities measured by the Charlson’s index and HTD as independent variable.

Results

A total of 32 515 out of 3 952 018 (0.8%) cases of HTD were found with a 66% of women vs 41.7% in NHTD (P < 0.001). Mean age was 77 (s.d. 12.71) years vs 72 (s.d. 17.06) in NHTD. Atrial fibrillation was more common in HTD (41% vs 22%; P < 0.001), and heart failure was more frequent in HTD (33% vs 21%; P < 0.0001). The mortality rate in HTD was lower than in NHTD (8% vs 10%; P < 0.001). In the logistic regression analyses adjusted by age, sex, and Charlson’s morbidity index, HTD was found to be an independent factor to prevent mortality in inpatients OR 0.69 (CI: 0.66–0.74; P < 0.0001).

Conclusions

HTD patients admitted to Internal Medicine wards have a lower mortality than NHTD. The frequency of women, atrial fibrillation and heart failure was higher in the HTD group. It is still unknown why HTD patients show lower mortality during admission. Perhaps other clinical and therapeutical factors, which have not been assessed through this retrospective study, have been involved with the hospital prognosis.

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Analysis according to severity of hyponatraemia between groups. Normo-na-traemia (135–144) 60.5%, mild (130–134) 21.7%, moderate (120–129) 15.3%, severe (<120) 0.6%, and hypernatraemia (≥145) 1.9%. Distribution of hyponatraemia among groups were as follows: SCLC mild 27.5%, moderate 21.6%, and severe 0% ; NSCLC: mild 19.8%, moderate13.4%, and severe 0%. The risk of death within 30 days was 43% higher in the hypona-traeicm group than the normoonaтраemic, not statistically significant. Normoanaemia 37.9%, hypona-traemia 46.6%, and odds ratio (95% CI) 1.43 (0.90–2.28), P = 0.13. The risk of death within 30 days in the mild and moderate groups increased by 46 and 27% respectively compared to normoanaemia but not statistically significant. Within 30 days – normoanaemia 117/190 (61.6%), mild 36/68 (52.9%), moderate 27/48 (56.3%), and severe 0%. Odds ratios: normoanaemia 1.00, mild 1.46 (0.83–2.55), P = 0.19; moderate 1.27 (0.67–2.42), P = 0.46, and severe NA.

Conclusions

Hyponaemia is a negative prognostic indicator in lung cancer patients. Further studies are needed to see whether correction of hyponaemia has any survival benefit.

Disclosure

The presenting author has received educational grant from Otsuka.

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EP1084

Somatostatinoma in patient with neurofibromatosis 1 – case report

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Introduction

We present a rare case of 49-year-old patient with neurofibromatosis type I and somatostatin-secreting pancreatic neuroendocrine neoplasm. World literature describes about 30 cases of duodenal somatostatinoma in NF1 and 1/3 of these cases with metastases to the lymph nodes or liver.

Case report

In October 2013 patient was operated in emergency due to gastrointestinal tract obstruction. During the procedure inoperable head of pancreas tumour, closing duodenum was confirmed. Gastrojejunitisostomia was performed, specimens from pancreas tumour were taken. Neoplasm tissue wasn’t found in the examined specimens in the histopathological examination. In June 2014 core biopsy pancreas tumour was performed under control CT which resulted in discovering neuroendocrine neoplasm G2. Afterwards in 30th September 2014 patient was operated (using the method of Whipple’s). Diagnosis well-differentiated neuroendocrine neoplasm G2, Ki-67 5% was confirmed (positive somatostatin reaction/expression in immunohistochemical test). In abdominal CT 17th December 2014 local recurrence and metastases to liver and lymph nodes have been identified. Stomachache, weight loss and loose stools (4/day) since October 2014 were appeared. Evaluated concentrations of neuroendocrine markers (CgA, insulin, gastrin, serotonin and 5-hydroxyindoleacetic acid) were in reference ranges. Determination of serum somatostatin level was impossible. Due to symptomatic and metastatic characters neuroendocrine neoplasm patient was treated with the somatostatin analogue. Clinical improvement (weight stabilization, diarrhea withdrawal) was observed.

Conclusion

Somatostatin-secreting pancreatic neuroendocrine neoplasm occurs very rarely and affects patients with neurofibromatosis type I. Somatostatin analogues in neuroendocrine neoplasm treatment resulted in great effectiveness.

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EP1085

Insulinoma: a multicentre and retrospective analysis of the Spanish experience during three decades

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Objective

To characterise insulinoma diagnosed and treated in the period 1983–2014 in various hospitals in Spain.

Methods

Inclusion criteria were the presence of biochemical and morphological criteria compatible with insulinoma and/or histologic demonstration of tumour.

Results

Twenty-nine patients (23 women (79.3%); mean age 48.7±17.4 years (range, 16–74)) were recruited. In 26 (89.7%) cases the tumor was sporadic and the rest (3 women, 10.3%) was presented in the context of multiple endocrine neoplasia (MEN 1). There were 3 (10.3%) multiple insulinomas, one associated with MEN and 2 (6.9%) sporadic malignant insulinomas. The majority (n = 18, 62.1%) showed fasting hypoglycaemia, about a third (31%) both postprandial and fasting hypoglycaemia and 6.9% postprandial hypoglycaemia only. Time to reach nadir of glucose (37.3 ± 6.5 mg/dl) in the fasting test was 9.0±4.4 h, with maximal insulinemia of 25.0 ± 20.3 mcU/ml. Abdominal CT detected insulinoma in 75% of patients. Twenty seven (93.1%) patients underwent surgery (enucleation, 18 (66.7%) and subtotal pancreatectomy was performed in 9 (33.3%) patients; mean tumour size was, 1.7±0.7 cm). Surgery achieved cure in the majority (n = 24, 88.9%) of patients.

Conclusion

Insulinoma is usually a benign, small and solitary tumour, affecting predominantly women aged 45–50 years which is habitually located with abdominal CT. Open surgery by enucleation is the most commonly used surgical technique achieving a high cure rate.

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EP1086

Psoriatic patients have not an increased risk of polycystic ovary syndrome-results of a retrospective study

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Objective

There are a few studies regarding the relationship between psoriasis and polycystic ovary syndrome (PCOS). The aim of present study was to identify the prevalence of PCOS in patients with psoriasis.

Material and methods

A retrospective study has been performed upon 1236 patients diagnosed with psoriasis (male 54.13%, female 45.87%) during 2004–2011. The prevalence of polycystic ovary syndrome (PCOS) has been quantified.

Results

Out of the 1236 patients diagnosed with psoriasis, 669 were men (54.13%) and 567 (45.87%) women. PCOS was diagnosed in eight patients, representing 1.5% of female patients of reproductive age with psoriasis.

Conclusion

Although previous data have suggested a higher prevalence of PCOS in women with psoriasis, our data does not support the correlation. Limitations of present study: no healthy age and body mass index (BMI)-matched controls.

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EP1087

Case report of successfully treated congenital hyperinsulinism in Armenia

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Introduction

Congenital hyperinsulinism is the most common cause for recurrent hypoglycaemia in neonates and infants. Uncontrolled hypoglycaemia leads to seizures and long-term cerebral damage. Herein, we report a case of congenital hyperinsulinism (persistent hyperinsulinaemic hypoglycaemia of infancy, neodioblastosis) and review of the relevant literature regarding on the aetiology, pathogenesis, clinical and pathological features, diagnosis and treatment of this disorder.
Case report
A term male newborn with a birth weight of 2900 g, delivered vaginally without complications, presented with tonic-clonic seizures and hypoglycaemia of 0.5 mmol/l (normal range 1.7–2.8 mmol/l) on the second day of life. Intravenous infusion of 12.5% glucose solutions at a rate of 10–17 mg/kg and dexamethazone 0.8 mg/kg were given to maintain a stable blood sugar level. The plasma insulin level was 32.3 μU/ml (normal values 2.6–24.9 μU/ml) and blood sugar level was between 0.5 and 7.2 mmol/l on day 30 of his life. These results suggest nesidioblastosis, or persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI). To confirm the diagnosis, the diagnostic laparoscopy was performed. During the surgery, enlarged hyperplastic Langergance islets were visualised, patient was subjected to a pancreatectomy with resection of 50% pancreatic gland. Pathological analysis was consistent with insulinoma. Conclusions and follow up
Congenital hyperplasia and dysplasia of pancreatic islet cells and a focal adenomatous hyperplasia was diagnosed by pathological analysis of surgical material, as well as clinical presentation. At present time, the patient is 3 years old, maintains euglycaemia with fractionated feeding and has a normal psychomotor development. This is the first case of diagnosis and successful treatment of congenital hyperinsulinism in Armenia.

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EP1088
Hodgkin's lymphoma presented as goitre: case report
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Introduction
Lymphomas account for <5% of thyroid malignancies. The vast majority of them are non-Hodgkin’s lymphomas (NHL), especially mucosa-associated lymphoid tissue lymphomas (MALT) and diffuse large B-cell lymphomas (DLBCL). However, Hodgkin’s lymphoma affecting thyroid gland is very rare. Worldwide has been reported <50 cases so far and we describe another one.

Case report
A 22-year-old woman was referred to our department of endocrinology for a rapid enlargement of thyroid gland. Prior short therapy of corticosteroids soothed the growth, but after its cessation the goitre enlarged causing dysphagia, dry cough and stridor. The patient also suffered with night sweats and intermittent fever. Both physical and ultrasound examination found unilateral large hypochogenic right thyroid lobe, deviating trachea to the left and at least two suspicious supraclavicular lymph nodes along the right sternocleidomastoid muscle. According to laboratory the patient was euthyroid, thyroid antibodies were negative, no significant changes in blood count. Elevated was lactate dehydrogenase (LDH 6 mkat/l), C-reactive protein (CRP 53 mg/l), erythrocyte sedimentation rate (ESR 76 mm/first hour). The fine-needle aspiration cytology (FNAC) was highly suspicious of lymphoma, but the flow cytometry did not prove any abnormal population of lymphocytes consistent with non-Hodgkin’s lymphoma. Therefore a diagnostic excision from the right thyroid lobe was performed. Final diagnosis of classical Hodgkin’s lymphoma, nodular sclerosing lymphoma. Therefore a diagnostic excision from the right thyroid lobe was visualised, patient was subjected to a pancreatectomy with resection of 50% pancreatic gland. Pathological analysis was consistent with insulinoma. Conclusions and follow up
Congenital hyperplasia and dysplasia of pancreatic islet cells and a focal adenomatous hyperplasia was diagnosed by pathological analysis of surgical material, as well as clinical presentation. At present time, the patient is 3 years old, maintains euglycaemia with fractionated feeding and has a normal psychomotor development. This is the first case of diagnosis and successful treatment of congenital hyperinsulinism in Armenia.

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EP1089
To be or not to be a primary hepatic neuroendocrine tumour
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Introduction
Primary hepatic neuroendocrine tumours (PHNTs) are a very rare medical entity. Usually, the liver represents the preferential site for metastasis. Large sized, singular nodules are the usual presentation of PHNTs. We report a patient with PHNTs at 4 years of tumour free follow-up.

Case presentation
A 45-year-old Caucasian female who presented with nausea, vomiting, diarrhoea, accompanied by diffuse abdominal pain, was found to have on contrast enhanced computer tomography an encapsulated liver mass measuring 7.8/5.9 cm, which contained multiple daughter cysts separated by a matrix. In this context, the initial diagnosis was of an Echinococcus cyst. The patient underwent an uneventful left atrypical hepatic resection. The resected specimen displayed a centrally brown-greyish solid cystic tumour measuring 8 cm, outlining a heavily vascularized cell proliferation with trabecular and band disposition and a homogenous growth pattern. The result of the immunohistochemical stain was diffusely positive for the tumour cells for chromogranin, synaptophysin and neuron specific enolase with 2–4% nuclear reactivity for Ki-67 index. Postoperatorically, the specific neuroendocrine markers (serum Chromogranin A and 24-h urinary-5-hydroxyindolacetic acid) were within the normal range. The patient underwent 111DTPA-ocrotetid scan, that showed no regions that were somatostatin receptor positive, and the PET scan with 5HTP could not find any suspicious lesions. The patient is now at 4 years of follow-up with no local recurrence or distant metastasis.

Conclusions
We report a case of primary PHNT in an adult female presenting with abdominal pain and diarrhoea, at 4 years of follow up with no signs of recurrence. We think that PHNT is an over-diagnosed medical entity, as most cases in English literature are incompletely documented, which makes it hard to establish the exact percentage of this type of tumour. In order to exclude an occult primary neuroendocrine tumour, thorough long-term investigations are required.

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EP1090
Benign and malignant thyroid disease in patients with acromegaly
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Introduction and purpose
Acromegaly is characterised by a chronic increase of GH and IGF-1 levels that may induce various clinical symptoms and multisystem comorbidities. The purpose of this study is to evaluate the type and frequency of thyroid disease most often associated with acromegaly patients.

Material and methods
We conducted a retrospective observational study analysing the data from the observation charts of 77 patients with acromegaly (58 females and 19 males), with a mean age of 54 years, evaluated between July 2007 and July 2014 in the Endocrinology department. The recorded data were: acromegaly status, sonographic thyroid morphology, thyroid function, and pathological data after surgical cure. The statistical analysis was conducted using Microsoft Excel 2010. Results
The acromegaly status was active for 49% of the patients, controlled in 37%, and cured in 14%. 96% of the patients were treated, the most common combination being surgical treatment + radiotherapy + medication (39%). Thyroid disease was diagnosed in 54 patients (70.12%). Nodular goiter had the highest prevalence rate (27.27%), followed by Hashimoto’s thyroiditis (12.98%) and thyroid cancer (10.38%). The occurrence of thyroid pathology was almost equal in women (70.68%) and men (68.42%). Thyroid disease was most frequent for the ≥ 60 years old age range, while acromegaly was most frequent in the 40–50 years old range. Other malignant diseases were diagnosed in 5% of the patients.

Conclusions
Thyroid disease is a frequent complication of acromegaly, with nodular goiter having the highest prevalence rate. In terms of malignant pathology, in our study, thyroid cancer had the highest prevalence rate (10.38%). This indicates the need for a systematic evaluation in order to achieve an early diagnosis.

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**EP1091**

**Mutation in CDKN1B 3'-UTR region in a patient with acromegaly and primary hyperparathyroidism**

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**Introduction**

Multiple endocrine neoplasia type 4 (MEN4) is a rare disorder, caused by inactivating mutations in CDKN1B gene that encodes p27Kip1 cyclin-dependent kinase inhibitor. To date nine different germline CDKN1B mutations have been described in patients with clinical features of multiple endocrine neoplasia type 1 (MEN1) negative for MEN1 mutations (MEN1 phenocopies). Case report

We present a female 54 y.o. with clinical features of MEN1: active acromegaly due to GH-producing pituitary macroadenoma after two consecutive neurosurgical interventions (transcranial and transsphenoidal) with remaining tissue in left cavernous sinus, requiring treatment with long-acting somatostatin analogues; mild primary hyperparathyroidism with ultrasound signs of superior right parathyroid adenoma; multinodular colloid goiter; extirpation of uterus and ovaries for adenomatous endometrial polyp, multinodular fibromyoma and endometrioid cyst; right mammary gland resection for benign lesion. Genetic testing for MEN1 germline mutation was negative. Genomic DNA from a blood sample of this patient together with ten other MEN1 phenocopies underwent high-throughput sequencing on the Ion Torrent Personal Genome Machine (Life Technologies) using a custom-designed AmpliSeq panel for the sequencing of a variety of genes, including CDKN1B, which could be responsible for the development of MEN1 phenocopies. We revealed a heterozygous mutation in 3'-UTR g.3897G>T (c.971G>T) in CDKN1B gene, which was in silico tested with free web-based application for disease-causing potential of DNA sequence alterations MutationTaster, detecting splice site alterations. Further in vitro studies are needed to confirm, whether this mutation alters protein function.

**Conclusions**

To our knowledge, we describe the first mutation in 3'-UTR of CDKN1B in a patient with MEN1 phenocopy.

**Disclosure**

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**EP1092**

**Analysis of current indications to bilateral adrenalectomy**

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**Introduction**

Bilateral adrenalectomy (BA) is rarely applied as a therapeutic procedure. It serves as a life-saving treatment in patients with persistent Cushing’s disease after an ineffective pituitary surgery or in ectopic ACTH production. Other indications for BA are: bilateral adrenocortical adenomas, congenital adrenal hyperplasia and bilateral pheochromocytoma in patients with hereditary paraganglioma-pheochromocytoma (PPS/PGL) syndromes. It is also a procedure of choice in bilateral adrenal metastases. The aim of the study was to determine the indications to BA in patients hospitalized in our ward between 2001 and 2012.

**Material and methods**

12 patients (7F: 5M) aged 19–72 years. Studies were based on retrospective analysis of medical records.

**Results**

Patients were divided into three groups. Group 1:7 patients (4F; 3M) with bilateral pheochromocytoma (MEN2 syndrome – four patients, PPS/PGL-1 patient, von Hippel – Linard – one patient, one woman with sporadic bilateral pheochromocytoma). Among three patients from group 2 the indications to BA were adrenal metastases of renal clear cell carcinoma in two and a metastasis to one adrenal gland coexisting with adenoma of the other in one case. Group 3: two women with Cushing’s disease. One of them was operated 31 years earlier proper corticotroph microadenoma and the second – because of atypical pituitary macroadenoma refractory to radiation, neurosurgical and pharmacological treatment. Patients with congenital disorders (sxs), Cushing’s disease (two) and one with metastasis and adenoma, underwent synchronous bilateral or two-stage adrenal surgery. Female with sporadic bilateral pheochromocytoma was operated twice at interval of 10 years and two patients with adrenal metastases at intervals of 3–4 years. Two patients died after a year and 3 years due to the progression of the underlying disease. The remaining are still alive (from 2 to 31 years after surgery).

**Conclusions**

Currently, the prevalent indication to BA is bilateral pheochromocytoma, mostly in the course of underlying hereditary neoplastic syndrome.

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**EP1093**

**Audit of adrenal tumours at Vilnius University Hospital Santariskiu Klinikos (VUHSK): 4 year results**

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The aim of study was to make a retrospective audit of diagnostic approach of symptomatic and asymptomatic patients with adrenal tumours diagnosed at VUHSK from 2010 to 2013.

**Methods**

Cases coded as D35.0; D44.1; E27.0; E27.5; E27.8; E27.9 according to ICD-10 classification were retrieved from database. Electronic data capture system was used to collect information.

**Results**

There were 527 (123 men, 404 women) patients, aged 62.5 ± 11 years, diagnosed with adrenal tumours from 2010 to 2013: 281 patient had symptoms; hypertension – 91.1%, episodic elevations of blood pressure – 34.5%, hypokalaemia – 18.1%, 246 patients had no symptoms. There were 71.5 and 94.7% of tumours found incidentally in symptomatic and asymptomatic groups respectively. Suspicion of hormonal hypersecretion and proper diagnostic approach was used only in 80 (28.5%) of symptomatic patients. Symptomatic patients were assessed for hormonal activity as compared to asymptomatic: aldosterone – 68.4 vs 43.9%, renin – 54.4 vs 30.1%, metanephrine/normetanephrine or adrenaline/noradreneline – 61.2 vs 22.0% (P<0.001 for all), cortisol – 39.2% in both groups, comprehensive analysis – 14.6 vs 6.5% (P=0.003). Computed tomography confirmed diagnosis in 93% of cases in both groups; with larger tumors in asymptomatic compared to symptomatic patients (24.7 ± 14.0 vs 22.5 ± 14.4 mm, P=0.02).

Non-secreting tumours were diagnosed in 81.4 vs 94.8%, aldosteroma – in 10.3% vs 1.2%, pheochromocytoma – in 6.8 vs 0.8% (P<0.001 for all), carcinoma – in 1.1 vs 0.4%, P=0.378 comparing symptomatic and asymptomatic groups respectively. There were 45% of secreting tumours in asymptomatic patients for whom proper diagnostic approach was used based on symptoms.

**Conclusions**

The proportion of patients having adrenal tumours with and without symptoms is similar. Although hormonal assessment should be performed in all patients, clinical symptoms should urge the doctor for comprehensive assessment as the prevalence of secreting tumours is the highest in symptomatic patients for whom proper diagnostic approach was used to clarify the diagnosis.

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**EP1094**

**Plasma chromogranin A and chromogranin B concentrations in untreated patients with mid gut carcinoid and their biochemical response to octreotide**

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We measured chromogranin A (CgA) and chromogranin B (CgB) in 36 patients, recently confirmed to have a mid gut carcinoid tumour (MGC), prior to the commencement of octreotide treatment. Blood samples were taken before and after a bolus injection of 50 µg octreotide. There were 21 males, 15 females, age range 28–76 median 61 years. Basal CgA, expressed as times the upper limit of normal (ULN) ranged from 333.3 to 0.5 ULN. Basal CgB ranged from 33.7 ULN to zero (undetectable). Of 36 patients, 21 had highly elevated basal CgA (> X5 ULN), ten had moderately elevated CgA (X2–X5 ULN) and five patients had normal or marginally raised
CgA. Nine patients had CgB > 2 ULN, four patients had elevated CgB up to X ULN and 23 had normal CgB. All patients with elevated CgB also had raised CgA. Fourteen of 29 patients with raised basal CgA showed a significant (>20%) decrease in CgA 60 min after octreotide injection. Three showed an increase of >20%. The remaining patients showed no significant change. Seven of 11 patients with a high basal CgB showed a decrease >20% 60 min post injection. It is generally observed that very high CgA concentrations before treatment begins may indicate advanced stage of disease and therefore poor prognosis. A lack of response may also predict a poor prognosis. However, good biochemical response to bolus octreotide may indicate a good future response to treatment. CgB was performed to assess its usefulness as a supplementary diagnostic test in neuroendocrine tumour patients with normal CgA. We did not observe any patients with raised CgB only according to the supplied kit reference range.

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EP1095
Endoscopic ultrasound features of familial vs sporadic pancreatic neuroendocrine tumours: a single-centre retrospective study
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Introduction Pancreatic neuroendocrine tumours (pNETs) can either occur in patients with a familial syndrome, like multiple endocrine neoplasia type 1 (MEN-1), or being sporadic. In the last decade, endoscopic ultrasound (EUS) has become one of the first-line investigations for the characterisation of pNETs. The ultrasonographic features of a pNET might differ depending on the familial vs sporadic pathogenesis of the tumour. Therefore, the EUS findings might help and direct the accurate definition of a pNET with a possible impact on the most appropriate diagnostic and therapeutic management of pNET patients.

Patients and methods In this single-centre retrospective study, we have reviewed the EUS characteristics of 131 pNETs from 38 MEN-1 patients and 14 pNETs from 13 sporadic disease patients at the time of their first EUS assessment. The patients attended consecutively our institution over a 5-year-time period. With the goal of defining the EUS features of MEN-1 vs sporadic pNETs, we have analysed the most relevant morphological and ultrasonographic aspects of the tumours and compared the findings between the two patient groups.

Results Patients with MEN-1 are more likely to present with multiple (3.4 vs 1.1 tumours/patient) and bigger (21.6 vs 7.5 mm) pNETs in comparison to those with sporadic disease. There is no statistical difference with regard to morphology, definition of the margins, and vascularization of the pNETs between the two groups. However, pNETs appear to be significantly more heterogeneous in patients with MEN-1 than in those with sporadic disease.

Conclusion In patients with MEN-1 pNETs tend to be more numerous, bigger, and more heterogeneous than in patients with sporadic disease. EUS can help with the precise characterisation of a pNET, including the definition of ultrasonographic features which can distinguish a familial vs sporadic disease.

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EP1096
Thyroid carcinoma in relation to gender and age in patient who were treated with total thyroidectomy for different thyroid disorders
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Aim of the study Thyroid cancer comprises the most common endemic malignancy and a variety of studies have examined the incidence of carcinomas in n thyroid disorders. Objective of the present retrospective study was the assessment of the possible influence of age and gender parameters in the presence of thyroid carcinoma in a patient who underwent total thyroidectomy.

Material and methods We studied 107 patients (96 females/11 males) underwent total thyroidectomy because of nodular goitre in our Department. The classification of patients in both genders was conducted in the following age-groups: a = 16–39 years, b = 40–59 years, c = > 60 years. Thyroid specimens were histopathologically examined at our Pathology Department for the establishment of the final diagnosis of benignity or malignancy. Thyroid cancer cases were categorized in relation to gender and age group.

Results 40 patients (37.3%) were diagnosed with carcinoma (rate females:males 9:1), while 67 patients (62.7%) were free of malignancy. The incidence of thyroid cancer in male subjects was 36.5% (4/11). The respective cancer frequency in female subjects was 37.5% (36/96). The incidence of carcinoma per age group was in males: a = 3/475, b = 0 and c = 1/5, 20%. In females it was respectively: a = 13/781, 48.1%, b = 2/2051, 39.2%, c = 3/18, 16.62%.

Conclusions

We found the highest prevalence of thyroid carcinomas among the females. Age-specific rates of thyroid carcinoma were higher among women than men across all age groups. In males groups there was a high incidence in the age group 20–39 years and >60 years. Total thyroidectomy appears to be the therapeutic method of choice in men with indication of surgical removement of a goitre which belong to the above age groups. Contrarily, there was a high incidence in women age group 15–39 with a pick 40–50 years.

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EP1097
The sensitising action of a TIM16 inhibitor towards chemotherapeutic agents in human breast cancer cells depends on TIM16 expression
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TIM16a component of the translocase complex TIM23 of the mitochondrial inner membrane is encoded by the Magmas gene. Magmas was found to be over-expressed in human pituitary adenomas. Silencing Magmas in ACTH secreting rat pituitary adenoma cells enhances sensitivity to pro-apoptotic stimuli. Moreover, Magmas overexpression protects GH secreting rat pituitary adenoma cell lines towards apoptosis. Recently, we found that compound 5, a TIM16 inhibitor, is not cytotoxic but enhances the proapoptotic effects of staurosporine by reducing mitochondrial membrane potential (MMP) activation in a medullary thyroid carcinoma cell line, suggesting that compound 5 may be useful for cancer treatment in association with chemotherapeutic drugs. Since breast cancer (BC) displays high chemoresistance, the aim of our study was to investigate Magmas expression in human breast cancer cell lines and to verify whether compound 5 could increase the effects of a chemotherapeutic agent, such as Doxorubicin in these cells. As an in-vitro model we used three human breast cancer cell lines: MCF7 and MDA-MB231 carcinoma cell lines and MCF12A normal breast cell line. We found that Magmas protein is highly expressed in the MCF7 cell line as compared to MDA-MB231 and MCF12A cells.

Our data show that treatment with compound 5 did not influence cell viability in the three cell lines, while Doxorubicin decreases this parameter by 20–30%. Only in MCF7 cells co-treatment with compound 5 enhances by 15–20% the antiproliferative effects of Doxorubicin, measured as cell viability and BrDU incorporation. MitoXox GlO assay shows that in MCF7 cells the enhancing effects of compound 5 on Doxorubicin action are due to mitochondrial toxicity. In summary, these data suggest a role for the use of compound 5 as a sensitising agent for chemoresistant breast cancer expressing high levels of TIM16.

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EP1098
Differential gene expression between primary and secondary hyperparathyroidism
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The pathophysiology differs significantly between primary and secondary hyperparathyroidism. Whole exome sequence analysis of parathyroid adenomas showed few somatic variants. The underlying mechanisms of the occurrence of sporadic primary hyperparathyroidism remain largely unknown. In this study, we analysed the differences in gene expression between primary and secondary hyperparathyroidism to explore potential functional alterations. Total RNA was extracted from tissues obtained during parathyroidectomy. Gene expression microarray and bioinformatic pathway analysis were performed. Parathyroid tissues were classified in an unsupervised manner into primary and secondary clusters. Parathyroid adenomas showed higher expression of cell adhesion molecules. On the contrary, secondary hyperparathyroidism exhibited upregulation of complement/coagulation cascades and mTOR signalling pathway. In conclusion, our study demonstrates that different pathophysiology led to differential gene profiling in hyperparathyroidism. The results from pathway analysis may have diagnostic and therapeutic implications.

Disclosure
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EP1099
Surgical correlation of thyroid nodules categorised as potential follicular neoplasms in core-needle biopsy (CNB)
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In our centre we use CNB for routine study of thyroid nodules since 2005. Four diagnostic categories for CNB’s results have been standardised: insufficient; benign; follicular proliferation (FOL), including follicular and oncocytic neoplasms; and malignant. Diagnosis of FOL was defined according to the presence of microfollicular patterned biopsies with scant or absent colloid, sometimes with minimal pleomorphism or discrete nuclear changes. This category could be equivalent to AUS/FLUS and FN/SFN, III and IV categories in BSRTC, encompassing undetermined diagnosis leading to surgical evaluation. We review surgical results in operated patients. A series of 166 patients (33 men, mean age, 52.8 years (SD 14.5) from 3750 CNBs (207 FOL; 5.5%) all of whom underwent surgery, from October 2005 to December 2014 were retrospectively analysed. They included 102 diagnosed as pure follicular lesions and 64 as oncocytic FOL. The false-positive rate, unnecessary surgery rate, and malignancy rate for the CNB patients according to the final diagnosis following surgery were evaluated. In surgical specimens 32 patients (19.3%) had non-neoplasms (unnecessary surgery), all of which were nodular adenomatous hyperplasia. The remaining 134 nodules were true neoplasms, 31 (18.7%) malignant. Malignant included 16 follicular carcinomas, 13 papillary carcinomas, one medullary carcinoma and one poor-differentiated thyroid carcinoma. In 23 cases there were incidentally discovered papillary carcinomas (1–12 mm of size) in the same or contralateral lobe of the biopsied lesion. From 102 adenomas, 17 carried an incidental PTC (16.7%). Globally, there were 54 carcinomas with a CB of FOL (32.5%). CNB shows good/fine precision in diagnosing follicular neoplasms, but as FNA, fail to distinguish adenomas from carcinomas, with a malignancy rate around 20%. We remark the frequent association of benign neoplasm (adenoma) with malignant lesions in the same thyroid (16.7%), supporting surgical treatment when this CB diagnosis is obtained.

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EP1100
Emotional state in men and women with acromegaly after pituitary adenomas
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Adult patients with acromegaly after pituitary adenomas usually have emotional problems, impaired quality of life. Objective was to detect possible differences of emotional state between patients with acromegaly after pituitary adenomas and healthy age- and sex-matched controls and to outline possible gender-specific differences.

Patients and methods
12 males (age 49.6±10.2 years) and 29 females (age 51.5±9.5 years) with acromegaly after pituitary adenomas; 12 control males (age 44.7±14.6 years) and 29 control females (age 50.4±12.7 years). Average duration since diagnosis of acromegaly was 7.1±8.9 years. Emotional state (domains of tension-anxiety, depression-dejection, anger-hostility, vigour-activity, fatigue-inertia, confusion-bewilderment) was evaluated using Profile of Mood States (POMS).

Results
Anger-hostility was significantly lower in men with acromegaly than in control men (9.5±5.0 vs 14.8±7.5, P=0.039). In women with acromegaly tension-anxiety (13.3±5.9 vs 4.5±6.0, P=0.005) was significantly higher than in control women. No significant differences in emotional state was detected between men and women with acromegaly and between men and women in the control group, only some statistical trends. In acromegalic patients there was statistical trend for men to have higher vigour-activity (16.8±4.8 vs 13.8±5.2, P=0.060) than women; in age- and sex-matched controls there was statistical trend for men to have higher anger-hostility (14.8±7.5 vs 9.7±5.7, P=0.061) than women.

Conclusion
Men with acromegaly after pituitary adenomas have lower anger-hostility level and women with acromegaly after pituitary adenomas have higher tension-anxiety level than age- and sex-matched controls.

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EP1101
Von Hippel–Lindau disease: report of two cases
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Introduction
Von Hippel–Lindau (VHL) disease is a rare autosomal dominant syndrome (1/36 000 live births) with highly penetrance that predisposes to the development of benign and malignant, highly vascularised tumours in many organs.

Case reports
Two women with VHL, without family history of VHL, were admitted to Department of Endocrinology for checkups. The diagnosis was made based on genetic tests.

Patient A
A 53-year-old woman, after partial right adenalecctomy in 1976 and total left adenalecctomy in 1979 due to bilateral pheochromocytoma. At present, she has no hypertension and typical symptoms of adrenal insufficiency. Hormonal tests revealed normal concentrations of serum cortisol and 24 h urinary cortisol in the presence of elevated serum ACTH that may indicate low adrenal reserve. The administration of hydrocortisone (10–20 mg/day) was recommended, in case of stress. The levels of serum chromogranin-A, dopamine and noradrenaline as well as 24 h urinary methoxycatecholamines were in normal range. All body scintigraphy and abdomen CT scan did not show pheochromocytoma recurrence.

Patient B
A 44-year-old woman, with right retina haemangioblastoma leading to blindness, after resection of cerebellum haemangioblastoma (with right hemiparesis and imbalance) and clear-cell carcinoma of the left kidney, with renal cysts. At present, she has no hypertension. Hormonal tests revealed normal concentrations of serum ACTH and cortisol and 24 h urinary cortisol as well as serum chromogranin-A, dopamine, noradrenaline, urinary 5-HIAA. Abdomen CT scan showed hepatic vascular malformations and two pancreatic tumours. In head MRI

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scan, the lesions: in right frontal lobe and in right eyeball were found. Somatostatin receptor scintigraphy confirmed increased radiolabelling accumulation in pancreas and in right orbit. We excluded pheochromocytoma. The diagnosis of pancreatic NETs, without hormonal activity, was made and the surgery is considered. Moreover, stereotactic radiotherapy for brain lesion was recommended.

Conclusions

Some manifestations of VHL cause that endocrine care is needed to optimize patients’ treatment.

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**EP1102**

**Enucleation of pancreatic proinsulinoma: case report**

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Introduction

Functional islet β-cell tumours represent 1–2% of all pancreatic neoplasms. Diagnosing this type of tumour is often challenging because they present with unspecific clinical features overlapping more common syndromes. Diagnosis involves expensive testing, so, establishing whipple’s trial and excluding causes of exogenous hyperinsulinism is crucial before initiating investigation.

Objective

To report a rare case of a proinsulinoma.

Case report

A 47-year-old woman was sent to the endocrinology department for evaluation of suspected spontaneous hypoglycaemia. There were no relevant antecedents. For 2 years she had had adrenergic/neurolipocicopic symptoms that relieved after ingestion of carbohydrate. She had gained 20 kg/2 years. Fractionated-diet, excluding simple carbohydrates, failed to improve symptoms. The patient was taught how to use a glucose meter to measure capillary blood glucose (BMT) and instructed to do a diary, that include meals content and BMT during symptoms. Study revealed hypoglycaemias (BMT 50 mg/dl) without a predictable pattern. Laboratory investigation confirmed endogenous hyperinsulinism secondary to autonomous proinsulin secretion. A study with CT-scan-with-contrast, ultrasound and endoscopy, showed a single oval nodule with 17 × 13 mm. Given the nodule to be unique and with very suggestive features of proinsulinoma, it was decided not to perform aspiration cytology. The patient started treatment with diazoxide while waiting for surgery. In September of 2014, she underwent a tumour enucleation, without complications. The histopathological study confirmed a low-grade neuroendocrine tumour. In the postoperative period symptoms/hypoglycaemia resolved and there was no hyperglycaemia or diabetes mellitus.

Conclusion

The work-up of fasting hypoglycaemia is crucial because a wrong diagnosis can lead to unnecessary pancreatectomy or a missed pancreatic tumour. Localisation is challenging so imaging studies should only take place once the diagnosis has been established. Highly specific serum insulin assay can difficult the diagnosis. An enucleative approach minimises the risk of developing post-operative diabetes, leading to a favourable prognosis.

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**EP1104**

**Adult-onset nesidioblastosis causing hyperinsulinaemic hypoglycaemia: diagnosis and treatment challenge: a case report**

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Nesidioblastosis is defined as a diffuse proliferation of primitive pancreatic islet cells budding from ductal epithelium. This condition can cause hypoglycaemia in infants as a result of mutations in the sulfonylurea receptor or in the anatomically linked potassium channel. In adults, this disease occurs independently from these genetic mutations.

Case report

A 41-year-old male was referred to our center via emergency room with suspicion of an insulinoma after an episode of loss of consciousness with a glycemia (G) of 24 mg/dl. Further questioning revealed three similar episodes in 2012. At admission: altered general status with retrograde amnesia, dry skin and mucous membrane and deep tenderness in the epigastrium, pulse 65 b/min. The 72 h fast was stopped for symptomatic hypoglycaemia with high insulinemia. Imaging studies were normal excepting endoscopic ultrasound which revealed a pseudolobular aspect in the pancreas tail and body. The patient was guided to a surgical clinic with dietetic recommendation and phenytoin 200 mg/day for insulinoma localization and surgical treatment. His was admitted into the surgical clinic after 3 weeks from the previous hospitalization with only two moderate hypoglycaemic episode under phenytoin treatment. The short octreotide test was interrupted due to symptomatic hypoglycaemia confirming the lack of tumour somatostatinoma receptors. Exploratory laparotomy was performed with intraoperative ultrasonography which exhibited two tumors in the pancreas tail and body. A subtotal spleno-pancreatectomy was performed. Microscopic view was consistent with nesidioblastosis and no tumour was found. The patient remains euglycaemic 10 months post-operatively.

Discussions

Nesidioblastosis is a rare cause of adult hypoglycaemia. Pre-operative differentiation from insulinoma is difficult, but mandatory when imaging studies are negative. New diagnostic tools like 18F-DOPA PET scan or selective arterial calcium stimulation with hepatic venous sampling (unavailable in our country) could help establishing the diagnosis.

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**EP1103**

**Morphological features and functional activity of parathyroid adenomas**

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Study for morphological and hormonal changes in the parathyroid glands in 35 patients with primary hyperparathyroidism was carried out. Post-mortem material (five bodies) used to control. All patients had primary hyperparathyroidism and elevated levels of parathyroid hormone and ionized calcium in serum. Morphometric study evaluated the cellular structure (chief and oxyphil cells) and calculated the ratio of the basic elements of parathyroid cells (nucleus, cytoplasm) and stroma (collagen fibres, blood vessels). The correlation between hormonal and morphological parameters calculated using the methods of variation statistics. Levels of PTH had significant variation range from 96 to 2665 pg/ml (X = 734, 6 pg/ml), as well as the volume of parathyroid adenomas – from 0.3 up to 31.5 cm3 (X = 5.1 cm3). A direct relationship is between the level of PTH and a relative density of nuclear component parenchyma (r = 0.56; P = 0.009). A feedback is between PTH and a relative density of parathyroid cells cytoplasm (r = −0.56; P = 0.012). There is no correlation between the level of PTH and the average number of cellular elements in the field of view (r = 0.27; P = 0.26). In parathyroid adenomas smaller than 1 cm3 of correlation between levels of PTH and the increase in the size of the tumour is not (r = 0.25; P = 0.47).

In parathyroid adenomas larger than 1 cm3 PTH level increases with tumour volume (r = 0.55; P = 0.01). There is no direct correlation between level of PTH and specific morphological changes in the parathyroid glands. Secretion of parathyroid hormone depends on the intracellular and the structural changes in parathyroid adenomas. Significantly changes are correlate with the size of the tumour.

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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±14.8 years, with a male to female ratio of 2:1.

Results

Apoplexy revealed an unknown adenoma in 74%. 48% were prolactinomas, 22% were GH-secreting adenomas and 30% were non-functioning adenomas. The commonest presenting symptoms were frontal and retro-orbital headaches in 92%, visual impairment in 78%, vomiting in 43% and oculovascular palsies mainly the third nerve palsy in 40% with diplopia and ptosis. Fever, meningeal irritation signs, rhinorrhea and epistaxis were reported in 8%. Predisposing factors were diabetes in 31%, bromocriptine use in 22%, antithrombotic medication in 4.3% and pregnancy in 4.3%. Pituitary imaging 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%. Endocrine evaluation showed at least one hormone deficiency in 92%. Gonadotroph deficiency was present in 78%, corticosteroid deficiency in 70% and thyrotroph deficiency in 61%. After the apoplexy episode 40% of GH-secreting adenomas normalized their GH-IGF1 levels and 27% of prolactinomas normalized their prolactin levels. Six patients were treated with high dose glucocorticoids with complete neuro-ophthalmological recovery in 67%.

Conclusion

Pituitary apoplexy is a rare life-threatening clinical syndrome caused by infarction or hemorrhage within a pituitary adenoma, once diagnosed a multidisciplinary team approach is mandatory in order to improve the outcome of this condition.

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Gastrintestinal stromal tumour in a patient with multiple endocrine neoplasia type 1

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Introduction

Multiple endocrine neoplasia type 1 (MEN-1) is an autosomal dominant disorder MEN-1 diagnosis is established as the occurrence of two or more MEN-1 associated tumour or one MEN-1 associated tumour in a patient that have 1 MEN-1 family member or positive MEN-1 genetic mutation. MEN-1 associated tumours usually involve the parathyroid glands, anterior pituitary and enteropancreatic cells but many other tumours may be seen. In this report, we presented a gastrointestinal stromal tumour (GIST) in a patient with MEN-1.

Case

A degree relative of a patient that has MEN-1 was hospitalised to our clinic for screening MEN-1 related tumours. The patient has stomach ache for 6 months and a history of gastric surgery for perforation 9 years ago. In his family history, one brother was diagnosed as MEN-1 (parathyroid adenoma, Cushing’s disease, gastric neuroendocrine tumour, pancreatic mass and positive MEN gene mutation) and other siblings are under evaluation for MEN-1 associated tumours.

Gastrointestinal stromal tumour (GIST) is a mesenchymal neoplasm that arises from interstitial cells of Cajal and may occur anywhere in the alimentary tract. They arise from the mesenchymal cells of the stomach, which are known as interstitial cells of Cajal. GISTs are neoplasms arising from connective tissue located in the gastrointestinal tract. They are composed of mesenchymal cells. The majority of GISTs are benign, but a small proportion can be malignant. GISTs are often asymptomatic and are usually discovered incidentally. However, they can cause symptoms such as abdominal pain, nausea, vomiting, and weight loss. Diagnosis of GIST requires histological evaluation, which often involves surgical excision or biopsy. The decision to treat GIST depends on several factors, including the size of the tumour, its location, and whether it is symptomatic or asymptomatic. Treatment options for GIST include surgical resection, chemotherapy, and targeted therapy.

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The micropenis: about a series of 30 patients

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Introduction
MEN1 is a rare syndrome characterised by hyperplasia or neoplasm of the parathyroid glands, pituitary, pancreas or duodenum and can associate, less frequently, phaeochromocytoma, thymic or bronchial carcinoids, multiple lipomas, cutaneous angiobromas and thyroid adenomas.

Case report
A 47-year-old woman with MEN1 presenting parathyroid recurrent adenomas, a pituitary prolactin-growth hormone co-secreting macroadenoma, associated with an incidentally papillary thyroid microcarcinoma. The patient had a primary hyperparathyroidism treated 12 years ago, diagnosed after she was treated for a coralliform lithiasis. 2 years after, a secondary amenorrhoea followed, caused by pituitary prolactin secreting macroadenoma, and a dopamine agonist was started. She didn’t present for the follow ups for 10 years, when another kidney stone was discovered. Laboratory results show hypercalcaemia and increased PTH, with normal TSH and free thyroxine levels. She had a total thyroidectomy and parathyroidectomy. Besides the two parathyroidian adenomas, the histopathological examination revealed a papillary thyroid microcarcinoma. 1 year after, she was admitted in our service. Having a MEN1 patient, we had to continue the investigation. We found a slightly increased PTH level with normal calcaemia, most probably secondary to the vitamin D insufficiency. The pituitary check-up showed a 1.01/1.03 cm adenoma with increased prolactin level and surprisingly increased IGF1 levels. She didn’t present for the follow ups for 10 years, when another kidney stone was discovered.

Discussion
Obesity is confirmed as breast cancer risk factor in postmenopausal women. The sensitivity to hormone therapy appear to be more efficient in PoBC women with BMI ≤30 compared to PrBC patients, and reveal their efficiency to decrease plasma oestradiol, leading to activate positive feedback mechanism on LH and FSH secretion.

Disclosure
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EP1112
Vitamin D and breast cancer
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Introduction
The anticancer action of vitamin D is currently considered one of its main properties. The main actions of vitamin D are related to the regulation of calcium levels and the normal function of the musculoskeletal system. However, its anticancer action is currently in the focus of research interests.

Aim
The aim was to study the effect of vitamin D on MCF-7 human breast cancer cells in vitro.

Methods
The effect of 1,25(OH)2D3 (Sigma-Aldrich) at an initial concentration of 200 nM on MCF-7 human breast cancer cells was studied. MCF-7 human breast cancer cells were incubated for 48 h at a temperature of 37 °C with progressively decreasing concentrations of 1,25(OH)2D3. MCF-7 cells were also incubated with progressively decreasing concentrations of 1,25(OH)2D3 (the initial concentration of 1,25(OH)2D3 being 200 nM) in the presence of the antimitotic agent docetaxel 50 nM.

Results
A mild inhibition of the proliferation of human breast cancer cells MCF-7 was observed after 48 h incubation with 1,25(OH)2D3. After simultaneous incubation with 1,25(OH)2D3 and docetaxel intense inhibition of the proliferation of MCF-7 breast cancer cells was observed.

Conclusions
In conclusion, a mild inhibitory effect of 1,25(OH)2D3 on the proliferation of MCF-7 human breast cancer cells was observed, while the antimitotic agent docetaxel had intense inhibitory effect on their proliferation. These findings are in agreement with the expression of VDR (Alimirah et al., Mol Cell Biochem, 2010), the vitamin D receptor, in breast cancer cells.

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EP1114
The effect of melatonin on pC3 prostate cancer cells in vitro
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Introduction
Melatonin is an indole being produced by the pineal gland and secreted mainly during the night. Melatonin is involved in the regulation of biological rhythms. The hormone possesses antioxidant action and is thought to be involved in the protection of the organism from the development of malignant tumors. Melatonin has been found to have anticancer action in vitro as is has been observed to inhibit the proliferation of cancer cells in vitro.

Aim
The aim was to study the effect of melatonin on PC3 prostate cancer cells in vitro.

Methods
The effect of melatonin (Sigma-Aldrich) at an initial concentration of 1nM on PC3 prostate cancer cells in vitro was studied. PC3 cells were incubated in vitro for 48 h at a temperature of 37 °C with progressively decreasing melatonin concentrations. PC3 cells were also incubated for 48 h with progressively decreasing melatonin concentrations in the presence of the antimitotic agent docetaxel 50 nM.

Results
The proliferation of PC3 prostate cancer cells was significantly inhibited by melatonin. In the simultaneous presence of melatonin and docetaxel the inhibitory effect on the proliferation of PC3 cells was very significant.

Conclusions
In conclusion, it appears that melatonin has an inhibitory effect on the proliferation of prostate cancer cells in vitro. These findings need to be confirmed in various other cancer cell lines and are in agreement with other research findings having shown the anticancer effect of melatonin. It appears that the modern way of life which disturbs the biological rhythms controlled by the cycle of light and inadvertently exposes the human organism to light during the night may contribute to carcinogenesis.

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EP1116
Expression analysis of potentially MEN1-targeting microRNAs in sporadic and MEN1 syndrome associated parathyroid adenomas and hyperplasias
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Background and aim
Primary hyperparathyroidism (PHPT) is a frequent endocrinopathy among postmenopausal women, leading to hypercalcaemia, osteoporosis and nephro lithiasis. PHPT may represent the first manifestation of certain familial syndromes. Among these, multiple endocrine neoplasia syndrome type 1 (MEN-1) caused by germine mutation of MEN1, the gene encoding menin, is the most frequent. Additionally, somatic mutations of MEN1 and microRNAs silencing MEN1 have also been proposed to be involved in sporadic parathyroid tumourigenesis. Our aim was to determine if there is a difference in expression of potentially MEN1-targeting microRNAs between MEN1 syndrome associated and sporadic PHPT tissues.

Materials and methods
In silico analysis was performed to detect microRNAs potentially targeting MEN1. Immunohistochemical analysis of menin and Ki67 was performed in 16 MEN-1 associated and 41 sporadic PHPT tissues. RNA was isolated from formalin-fixed, paraffin-embedded PHPT tissues and microRNA expression analysis of six microRNAs was performed using predesigned TaqMan probes for quantitative PCR. MEN1 status was determined by Sanger sequencing. Statistical analysis was performed using IBM SPSS Statistics Software.

All MEN-1 associated as well as 12 (29.3%) sporadic PHPT tissues lacked nuclear menin expression on immunohistochemical analysis. MicroRNA analysis revealed that hsa-miR-24 and hsa-miR-28 levels were elevated in sporadic PHPT tissues compared to those measured in MEN-1 associated tissues (P=0.011 and P=0.019, respectively).

Conclusions
Elevated levels of microRNAs potentially targeting MEN1 detected in sporadic PHPT tissues might contribute to the silencing of menin during sporadic parathyroid tumourigenesis.

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EP1117
Vitamin D and prostate cancer
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Introduction
Vitamin D is a hormone related to calcium homeostasis and normal function of the muscoskeletal system. Recently, the extraskeletal actions of vitamin D are the focus of scientific interest. The hormone is thought to possess anticancer properties, these properties being especially related to cancer of the prostate.

Aim
The aim was to study the effect of vitamin D on PC3 prostate cancer cells in vitro.

Methods
The effect of 1,25(OH)2D3, 25(OH)D3, 1α(OH)D3 and paricalcitol at initial concentrations of 200, 40, 20 and 20 nM, respectively, on PC3 prostate cancer cells was studied in vitro. PC3 cells were incubated for 48 h at 37 °C with progressively decreasing concentrations of 1,25(OH)2D3, 25(OH)D3, 1α(OH)D3 and paricalcitol. Experiments were also performed with 1,25(OH)2D3 at concentrations of 500 nM and 1 μM. PC3 cells were also incubated with progressively decreasing concentrations of 1,25(OH)2D3, the initial concentration being 200 nM, in the presence of the antimitotic agent docetaxel 50 nM.

Results
The proliferation of PC3 prostate cancer cells was not affected by 25(OH)D3, 1α(OH)D3 and paricalcitol at initial concentrations of 200, 40, 20 and 20 nM, respectively, on PC3 prostate cancer cells was studied in vitro. PC3 cells were incubated for 48 h at 37 °C with progressively decreasing concentrations of 1,25(OH)2D3, 25(OH)D3, 1α(OH)D3 and paricalcitol. Experiments were also performed with 1,25(OH)2D3 at concentrations of 500 nM and 1 μM. PC3 cells were also incubated with progressively decreasing concentrations of 1,25(OH)2D3, the initial concentration being 200 nM, in the presence of the antimitotic agent docetaxel 50 nM.

Conclusions
In conclusion, 25(OH)D3 and analogues of vitamin D had no effect on the proliferation of PC3 prostate cancer cells. However, relatively high concentrations of the active hormone 1,25(OH)2D3 was shown to inhibit PC3 cells proliferation. It appears, that vitamin D may possess anticancer properties especially related to prostate cancer.

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EP1118
Oestrogen- and progesterone-receptors may play a role in the pathogenesis of gastroenteropancreatic neuroendocrine tumours
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A positive expression of oestrogen-receptors has recently been demonstrated in pancreatic neuroendocrine tumours as well as in non-neoplastic islet-cells. This prompted us to systematically analyse the expression of both oestrogen and progesterone receptors in a series of GEP neuroendocrine tumours. We analysed...
Audit of patients with multiple endocrine neoplasia type 1 (MEN1): screening of pancreatic neuroendocrine tumours (pNETs), parathyroid tumours and pituitary adenomas

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Introduction
Patients with MEN1 have increased morbidity and mortality compared to those patients with sporadic NETs. No genotype-phenotype correlation is described and age-related clinical penetrance surpasses 50% and 90% by 20 and 40 years, respectively. The aim of the audit was to compare the screening programme for MEN1 patients with MEN1 clinical guidelines.

Methods
Case notes of MEN1 patients attending a tertiary NET-multidisciplinary team (MDT) in Ireland were reviewed. All patients attending the NET-MDT have gastrointestinal hormone, parathyroid, pituitary profiles, endoscopic and imaging studies according to guidelines (NH1 2012, Brandi et al. 2001; 86; 5658–71).

Results
Of 13 patients with MEN1 (11 kindreds), 85% (n=11) had confirmed MEN1 mutations and two had clinical or familial MEN1, 69% were referred to NET-MDT for screening due to known MEN1 mutations, 15% for family screening, 8% for management of pNETs and 8% for screening due to primary hyperparathyroidism (n=11, 6.1%), breast cancer (n=5, 4.6% of women with acromegaly) and colonic cancer (n=4, 2.2%).

Conclusions
Patients with acromegaly present increased risk of neoplastic transformation, especially in the thyroid, adrenal, gastrointestinal tract and prostate. Among malignancies, thyroid, breast and colonic cancer were the most frequent. According to our results, active screening for potential malignancies should be an important part in the management of acromegaly.

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Identification of human SST2 somatostatin receptor domains involved in receptor internalization and signaling in pancreatic neuroendocrine tumors

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Somatostatin exerts its inhibitory effects on hormone secretion and cell proliferation via five receptors subtypes (SST1–SST5). After agonist binding, receptor resides mainly located in the carboxyl terminal (CT) and in the third intracellular loop (IC3) are phosphorylated and β-arestatins are recruited to drive SSTRs internalization. The aim of the study is to characterize the intracellular mechanisms responsible for SST2 internalization and identify the molecular determinants mediating its intracellular signaling in pancreatic neuroendocrine GP1 cell line. To this purpose we created SST2 receptor mutants, the first lacking 20 aminoacids in CT portion (del349), the second a IC3 mutant with a point mutation (Ser245Ala) in a phosphorylation site. We evaluated SST2 mutants ability to associate with β-arestatins and to internalize after SST2 selective somatostatin analog stimulation (BIM23120). In cells transfected with the SST2 IC3 mutant, no differences in β-arestatins recruitment and receptor internalization were observed after SST2 activation in comparison with cells bearing wild type SST2. Conversely, the truncated SST2 failed to recruit β-arestatins and to internalize after BIM23120 incubation. Then, we analyzed the effect of BIM23120 on cell proliferation, cyclin D1 expression and ERK1/2 phosphorylation in the presence of either IC3 mutant and truncated SST2. As expected, BIM23120 induced a reduction in cell proliferation (~30±7%, P<0.01 vs untreated) and in CD1 expression (~23±8%, P<0.001 vs untreated) in SST2 wild type (QGP1) transfected cells, this effect being completely lost in the presence of both SST2 mutants. To further

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The prevalence of benign and malignant neoplasms in the patients with acromegaly

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Introduction
Acromegaly is a relatively rare endocrine condition caused by GH oversecretion by pituitary adenoma. Its most frequent complications include cardiovascular and respiratory system diseases with high tendency of neoplastic transformation and increased risk of benign and malignant tumors. The aim of this retrospective study was to assess the prevalence of benign and malignant neoplasms in patients with acromegaly.

Materials and methods
We have searched the medical documentation of patients treated in our medical center from the years 2004–2013. The prevalence of benign and malignant neoplasms was analysed basing on the latest available records of particular patients.

Results
We have identified 180 patients with acromegaly (108 women, 72 men). The mean age at the time of last available assessment was 52.5 years (S.D. 12.2, median = 54.0). The most common neoplastic comorbidity was observed in the thyroid (140 patients (77.8%) – 110 patients with multinodular goiter (MNG) (61.1%) or resection of MNG in the past medical history. Adrenal adenomas were diagnosed in nine subjects (%), prostate hyperplasia in six (8.3% of males), and polyps of the colon in 1.7% of all individuals. Among malignancies, the most common were thyroid cancer (n=11, 6.1%), breast cancer (n=5, 4.6% of women with acromegaly) and colonic cancer (n=4, 2.2%).

Conclusions
Patients with acromegaly present increased risk of neoplastic transformation, especially in the thyroid, adrenal, gastrointestinal tract and prostate. Among malignancies, thyroid, breast and colonic cancer were the most frequent. According to our results, active screening for potential malignancies should be an important part in the management of acromegaly.
analyze the antiproliferative actions of SST2, we analyzed the effects of SST2 activation on ERK1/2 phosphorylation and we found the both SST2 mutants fail to affect ERK1/2 phosphorylation status after BIM23120 incubation. Taken together these data suggest that: i) CT region is crucial for β-arrestins/SST2 interaction and SST2 internalization; ii) antiproliferative intracellular signaling mediated by SST2 require the integrity of both CT and IC3 domains.

Disclosure
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**EP1123**

Evaluation of routine basal serum calcitonin measurement for an early diagnosis of medullary thyroid carcinoma

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**Background**
Medullary thyroid carcinoma (MTC) is characterised by a high concentration of serum calcitonin. Routine measurement of serum calcitonin concentration has been advocated for detection of MTC among patients with nodular thyroid diseases. The aims of our study were to identify medullary thyroid cancer (MTC) in its earliest stages by screening patients with basal calcitonin measurements and to determine whether basal serum calcitonin measurements should be a part of our routine evaluation of a nodular goitre.

Subject and methods
We performed routine measurement of basal serum calcitonin levels from 151 patients (male 30 and female 121 with nodular goitre. The average age was 47 years old (range 19–76).

Results
Patients with FNAC or ultrasound suspicious of any kind of thyroid carcinoma and patients with elevated basal calcitonin level underwent surgery. Three patients (1.9%) had elevated basal serum calcitonin levels ranging between 129 and 7403 pg/ml. FNAC was suggestive of MTC in two from three patient with elevated calcitonin. MTC was confirmed in all patients, with elevated calcitonin. Differentiated thyroid carcinoma, mostly papillary, was confirmed at histology in 40 subjects. The prevalence of MTC, diagnosed by serum CT measurement among 136 patients with nodular thyroid disease was high: 1.9% of all thyroid nodules and 7% of all thyroid carcinomas. Serum CT measurement was superior to FNAC in suggesting the diagnosis of MTC.

In conclusion, calcitonin measurement is an effective method for the diagnosis of MTC. It is superior to FNAB for diagnosis of MTC. High basal serum calcitonin levels increase the chance of curative therapy by diagnosing it in the early stages.

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**Table 1** Demographic parameters in studied group.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53 ± 11.2</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>23 M/128 F</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>95.2 ± 17.1</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>152.1 ± 73</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>11.9 ± 0.67</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>2.6 ± 0.47</td>
</tr>
<tr>
<td>Parathormone (mg/dl)</td>
<td>253.8 ± 256.9</td>
</tr>
<tr>
<td>Metabolic syndrome (%)</td>
<td>50.3</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>15.2</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>72.8</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>52.3</td>
</tr>
<tr>
<td>Overweight (%)</td>
<td>35.7</td>
</tr>
</tbody>
</table>
triglyceride were 95.2 ± 17.1 and 152.1 ± 73 mg/dl, respectively. The rate of obesity, overweight was 52.3 and 35.7% respectively. There were no significant differences between the levels of calcium, phosphorus and parathormone levels (11.1±0.3 vs 11.01 ± 0.6 mg/dl, 2.59±0.45 vs 2.63 ± 0.48 mg/dl, 259.6 ± 238 vs 247.5 ± 276 mg/dl respectively) according to MS presence (Table 1).

Conclusion
Based on the results of this study, the rate of the MS in PH was found to be higher than that reported in the general Turkish population. Metabolic control must be considered in the clinical management of patients diagnosed PH.

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**EP1125**

**Mitotane directly interacts with lipid membranes and alters membrane structure and dynamics**

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**Context**
Mitotane (1,1-dichloro-2-[o-chlorophenyl]-2-[p-chlorophenyl]ethane) is the only drug approved for treatment of adrenocortical carcinoma (ACC). Mitotane counteracts both tumor growth and tumoural steroid hormone production but treatment is severely hampered by unfavorable pharmacokinetics and serious side effects. Mitotane is a lipophilic compound and treatment emergent alterations of lipid metabolism are frequently observed. This raises the question whether mitotane directly interacts with lipids.

**Objectives**
To investigate the impact of mitotane on lipid membranes using biophysical techniques.

**Methods**
We used nuclear magnetic resonance (NMR), electron spin resonance (ESR) and fluorescence spectroscopy as well as fluorescence microscopy to determine whether mitotane interacts with lipid membranes. We aimed at determining the impact of mitotane on membrane structure and dynamics by assessing its influence on membrane integrity and on the formation of lateral membrane domains in lipid vesicles (large unilamellar vesicles, giant unilamellar vesicles).

**Results**
We demonstrate that mitotane intercalates into lipid membranes. This binding influences the mobility of spin-labeled lipids within membranes and disturbs membrane integrity in a dose-dependent manner. The presence of cholesterol in the membrane appears to modulate these effects.

**Conclusion**
Mitotane directly binds to and interacts with lipid membranes thereby altering membrane structure and dynamics. This interaction may contribute to the biological effects of mitotane impacting both on efficacy and adverse effects.

**Disclosure**
This work was supported by the Deutsche Forschungsgemeinschaft (grant FA 466/4-1 to M.F. and KR 4371/1-1 to M.K.) and a fellowship of the Comprehensive Cancer Center Mainfranken to M.K.

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**EP1126**

**Oestrogen metabolism by steroid sulphatase and 17β-hydroxysteroid dehydrogenases promotes colorectal cancer proliferation via the G-protein coupled oestrogen receptor**

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Colorectal cancer (CRC) is the third most common cancer worldwide with incidence expected to rise. Although not traditionally viewed as a hormonal cancer, evidence suggests peripheral synthesis of active oestrogens worsens prognosis. Oestrogen metabolising enzymes include steroid sulphatase (STS), which desulphates oestrogens into their active forms, and 17β-hydroxysteroid dehydrogenases (17βHSD), which are estrogen oxidoreductase enzymes. We have previously shown STS activity is increased in human CRC compared to matched-normal tissue. However, the impact of this increased oestrogen de-sulphation on CRC proliferation is unknown. Furthermore, the expression and activity of 17βHSD-1, 17βHSD-7 and 17βHSD-12, all of which reduce the less active oestrone (E1) to the more potent oestradiol (E2), have not been fully examined in CRC. Thus, this project investigated the proliferative effects of E1 and E2 treatment and overexpression of STS in CRC cell lines. Additionally, how these cell lines metabolised oestrogen was analysed using a novel uPCL-MS/MS technique. Protein and mRNA expression of 17βHSDs capable of reducing E1–E2 were examined in human CRC tissue and cell lines. Oestrogen (E1 and E2) and STS overexpression increased proliferation of the CRC cell line HCT116. Proliferation also increased in response to G1, a G-protein-coupled estrogen receptor 1 (GPER) agonist. LC-MS/MS indicated HCT116 cells reduced E1–E2 most likely catalysed by 17βHSD-12. In human CRC 17βHSD-1 was not expressed, however 17βHSD-7 and -12 expression was significantly elevated (P < 0.0005) compared to matched normal tissue. GPER was also found to be expressed in the colon. Together these findings suggest the majority of human CRC escalate intratumoral E1 concentrations through STS and 17βHSD-12. This local oestrogen rise likely acts through GPER to augment tumour proliferation. Therefore, STS, 17βHSD-12 and GPER inhibitors may benefit many CRC patients.

**Disclosure**
Medical Research Council UK PhD Studentship. Society for Endocrinology Early Career Award.

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**EP1127**

**Expression of ghrelin and somatostatin systems components in pancreatic neuroendocrine tumours and their relationship with clinical-histological characteristics**

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Pancreatic neuroendocrine tumors (PNETs) are uncommon neoplasms from the endocrine pancreas, whose incidence is recently rising. Unfortunately, an advanced stage is often found at diagnosis; thus, identification of new molecular diagnostic, prognostic, and therapeutic markers is required. Ghrelin and somatostatin/cortistatin systems are two multifunctional regulatory complexes widely distributed throughout multiple tissues, including the pancreas, where they exert diverse (patho)physiological actions; and alterations in these systems can be associated to development/progression of various cancers. Here, we aim to evaluate expression levels of ghrelin and somatostatin systems components in PNETs and explore their putative relationship with histological/clinical patient features. Namely, an observational retrospective study with 28 PNET patients was performed by collecting clinical/histological characteristics and measuring expression levels of ghrelin and somatostatin/cortistatin systems components, by quantitative-PCR, in formalin-fixed paraffin-embedded PNET samples (n = 25; 52.2% G2, 43.5% G1 and 4.3% G3) and in control adjacent non-tumoral tissues. Mean age was 55 ± 14 years (57.1% females); 21.1% of cases were diagnosed incidentally, 42.1% were functioning tumors and 40.7% had metastasis at diagnosis. Tumour diameter associated negatively to vascular invasion (P < 0.05) and necrosis (P < 0.05). Somatostatin receptor (sst) subtypes-1 and -2, cortistatin and ghrelin O-acil-transferase enzyme were overexpressed in PNETs compared to control-tissues (P < 0.01). Presence of skin lesions at diagnosis was correlated to sst3 expression (P < 0.05). sst1 expression was negatively associated with vascular invasion (P < 0.05). Ghrelin-receptor was negatively associated with nerve invasion (P < 0.01). Mortality was associated to metastasis (P < 0.05), relapsed disease (P < 0.05) and somatostatin expression. Interestingly, there was a trend for mortality and sst3 expression to be associated (P = 0.08). Our results indicate that the majority of ghrelin and somatostatin systems components are expressed in PNETs, where some of these components
**EP1128**
A unique case of hyperparathyroidism-jaw tumour syndrome due to a previously unreported pathogenic duplication mutation of CDC73 gene

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Hyperparathyroidism-jaw tumour syndrome (HPT-JT) is a rare autosomal dominant condition characterized by primary hyperparathyroidism (<90%) as a result of parathyroid adenoma or carcinoma (10–15%), ossifying fibromas of mandible and maxilla (30–40%), renal lesions (20%) most commonly cysts and benign and malignant uterine tumours caused by germline CDC73 gene mutations. Currently only 200 cases reported in medical literature. His management has proved more difficult which may be associated with this novel CDC73 pathogenic gene mutation. A 31-year-old man presented with polydipsia, fatigue, corrected calcium of 4.3 and PTH 147. USS and CT neck revealed a left inferior parathyroid adenoma, confirmed by exploration. Histology showed disruption of the capsule with fibrous tissue extending into the lesion at one pole although no overt malignancy. A few months later he had recurrence of symptoms, further hypercalcaemia and a right inferior parathyroid adenoma was excised. Genetic testing detected a novel pathogenic duplication mutation of CDC73 gene leading to premature termination of translation. He presented a third time with hypercalcaemia. No adenoma was identified on imaging however he declined selective venous PTH sampling. His case was extensively discussed with multiple specialists with differing opinions as to total parathyroidectomy plus/− auto transplantation. Patient elected for total parathyroidectomy and no auto transplantation due to his germline CDC73 pathogenic gene mutation and 10–15% risk of parathyroid carcinoma development. This unique case illustrates consideration of genetic testing in primary hyperparathyroidism under 45 years, with challenges in rarity and management including implications for biopsy and surgical intervention, multisystem lifelong screening of proband and relatives which is recommended from 5 to 10 years and availability of predictive genetic testing for the familial CDC73 gene mutation. This indicates a significantly more complex case where previous literature has been unable to guide on management and may help advise other endocrinologists.

**EP1129**
Extremes in hyperparathyroidism: management of parathyroid carcinoma

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Background
Parathyroid carcinoma (PC) is a rare cause of primary hyperparathyroidism (PHPT), accounting for <1%, with an equal gender distribution and an average age of diagnosis in the fifth decade of life. The diagnosis of PHPT is based on the laboratory finding of high levels of immunoreactive PTH in the presence of severe hypercalcaemia. The only potentially curative treatment for PC is surgery. Early surgery is the most important factor for optimal outcome.

Methods
This case series is based on a multidisciplinary review of four patients with parathyroid carcinoma, describing their therapeutic management and follow-up. Imagistic evaluation was performed by ultrasound (US), computed tomography scan (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and Technetium-99m sestamibi scintigraphy, for detecting the primary tumour, its local extent and remote metastases.

Results
Between 2008 and 2014 four patients were diagnosed with PC in our clinical department, three men and a woman, with a mean age of 50 years ± s.d. 13.22 (range 38–68). None had family history of hyperparathyroidism or hormonal disorders suggesting multiple endocrine neoplasia. All had severe hypercalcaemia (15.3–19.4 mg/dl) and elevated PTH levels ranging from 15 to 45 times above normal value. Tumor size ranged from 3.2 to 7 cm; two of them had thyroid gland invasion and one thymic invasion. Three patients underwent parathyroidectomy with hemi thyroidectomy and one underwent parathyroidectomy with thyromectomy and cervical dissection. Schulte stage at diagnosis was between II and IV, while all were classified as high risk. Conformational radiotherapy of the tumor bed was used in two cases. Cinacalcet treatment was tried in one case and chemotherapy regimen in another, without significant improvement. Three patients had local recurrence and the time from the initial surgery to recurrence ranged from 1 month to 1 year.

Conclusion
Parathyroid carcinomas are rare endocrine cancers, with high relapse rate and poor prognosis. Multidisciplinary approach requires detailed imaging, skilled surgeons, endocrinologist and oncologist.
EP1131
Inhibitor of apoptosis protein Livin/BIRC7 in adrenocortical tumours
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Introduction
Adrenocortical tumours comprise frequent adenomas (ACA) and rare highly malignant carcinoma (ACC). Livin/ML-IAP/BIRC7 is a member of the inhibitors of apoptosis proteins family, which are involved in tumorigenesis, mostly through the inhibition of caspase-3. Aim of the study was to evaluate the expression of livin/BIRC7 in normal and neoplastic adrenal glands.

Methods
The mRNA expression of BIRC7, its isoforms livin α and livin β, and caspase-3 was evaluated by qRT-PCR in 84 fresh-frozen tissues (34 ACC, 25 ACA, 25 normal adrenal glands = NAG), including 19 paired samples of tumour and surrounding NAG. Additionally, livin protein expression was assessed by western blot analysis (WB) in 14 paired samples (eight ACA, six ACC) and by immunohistochemistry in 127 paraffin-embedded tissue sections (67 ACC, 45 ACA, 15 NAG). The relationship with several histopathological and clinical data was also evaluated.

Results
BIRC7 mRNA expression was similar between ACAs (0.01 ± 0.01) and NAG (0.01 ± 0.02), but significantly higher in ACCs (0.06 ± 0.12, P < 0.005 vs both ACA and NAG), the isoform β was more expressed than α in all the subgroups. Comparable results were obtained with WB. The caspase-3 was higher in ACA (0.024 ± 0.012) than in ACC (0.017 ± 0.011, P = 0.05) and NAG (0.018 ± 0.011, P = 0.03). Livin cytoplasmatic immunostaining was relatively homogeneous (79.5% of more than 50% positive cells). Livin protein expression was higher in ACC than ACA and NAG (mean ± s.d. H-score: 1.72 ± 0.7 vs 1.58 ± 0.5 vs 1.33 ± 0.6, respectively; P = 0.09), being even higher in ACC samples coming from first surgery (n = 53, 1.8 ± 0.7) than in those coming from recurrence (n = 8, 1.24 ± 0.5) or distant metastasis (n = 6, 1.5 ± 0.5) (P = 0.0001). No significant correlation was observed with the histopathological and clinical data, including overall survival.

Conclusion
Our study demonstrates that livin/BIRC7 is specifically over-expressed in ACCs suggesting that it may be involved in adrenocortical tumorigenesis. BIRC7 could represent a novel marker for malignancy and a potential target for therapeutic approaches in ACC.

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EP1132
High-dose treatment with somatostatin analogues in neuroendocrine tumours
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Somatostatin analogs (SSA) effectively control symptoms in neuroendocrine tumours (NET), besides showing antiproliferative activity. In progressive or metastatic NET, increasing SSA dose or shortening the dosing interval are common clinical practice, though empirical. Aim of this study is to evaluate efficacy and safety of high-dose SSA treatment in patients with progressive disease under standard SSA dose. Twenty-one patients (median age 56.3 years) with NET of different origin were retrospectively identified among 118 patients under SSA therapy. All 21 patients were treated with SSA high dose schedule treatment, after disease progression under standard dose. The median follow-up was 22.3 months (range 4–76). High dose schedule included octreotide LAR in 15 patients (73%) and lanreotide Autogel in 6 (27%). Progression free survival was significantly higher with high-dose treatment compared with standard dose (32 vs 8 months, P < 0.05). Partial objective tumour response was recorded in one patient (5%), stabilisation in 10 (47.5%) and progression in 10 (47.5%). Among 16 patients who were symptomatic under standard dose, complete clinical response was obtained in 1 (6%), partial response in 9 (57%). Side effects were abdominal discomfort (5%), asymptomatic gallstones (5%) and type 2 diabetes mellitus (5%). High-dose SSA treatment in progressive NET is still effective in patients refractory to standard SSA doses. No additional toxicity is observed compared with standard dose.

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EP1133
Cranioopharyngioma audit, single centre experience
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Objectives
Cranioopharyngioma is a benign tumour of the suprasellar region that is associated with increased morbidity and mortality in comparison to other causes of hypopituitarism. We aimed to establish the mode of presentation, investigations, treatment outcomes, mortality and subjective improvement in patients with craniopharyngioma in a single institution over 10 years.

Design
Retrospective case notes review of patients with Craniopharyngioma on endocrine register between 2000 and 2010. Clinical records of eligible patients were reviewed and information regarding clinical presentation, medical and surgical management and post treatment outcomes were extracted and collated.

Results
Symptoms at presentation: the commonest presenting symptoms were headache (79%) and visual impairment (75%). Other symptoms were vomiting (27%), cognitive dysfunction (3.4%), weight gain (34.4%), reduced conscious level (3.4%), poor energy level (68.9%), somnolence (13.7%), loss of libido (13%) and polyuria (13.7%).

Surgical outcomes
Gross total resection was achieved in 41.3% but was curative in only 20%. The remaining 80% required further surgical and/or radio therapeutic intervention. Reduction in tumour size was achieved in 86% of patients. CSF leak was 18% post surgical intervention. Visual field were fully recovered in only 27.8% and partially recovered in 26% of patients after surgery and radiotherapy. Endocrine outcome was complex: multiple pituitary hormone deficiency evolved in all patients over time, the commonest were hypothyroidism (79%) and ACTH deficiency (72%). Other deficiencies were gonadotrophins (45%), diabetes insipidus (41%), and GH deficiency (4%). Although neurocognitive, psychological and behavioural problems were noted for some patients, only 20% of patients were formally assessed. Subjective improvement in condition was assessed by follow up clinic letters that 59% patients have reported improvement in their condition but 18% of these patients got worse after intervention.

Mortality
All cause mortality was 31%. Tumour related mortality was 25%.

Conclusions
Cranioopharyngioma is associated with significant long-term morbidity. Attention to an integrated care pathway that includes standardised neurocognitive and psychological and behavioural assessment would facilitate early appropriate intervention and support leading to an improved quality of life of patients with craniopharyngioma.

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EP1134
Gonadotropin releasing hormone antagonist treatment induces cell cycle arrest in gonad al solid cell and adrenocortical tumours
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Gonadotropin releasing hormone analogues (GnRH-a) have been used in the treatment of several endocrine and non-endocrine conditions including cancer. In humans and animals, GnRH-a analogues cause a dose-dependent decrease in circulating gonadotropins (FSH and LH) but no significant changes in the serum levels of gonadal steroid hormones. They also act as a potent antiangiogenic agent and induce cell cycle arrest in gonadal and solid tumours (e.g. prostate and breast cancer). GnRH-a induces cell cycle arrest in gonadal and solid tumours by inhibiting the GnRH/GnRHR axis and consequent down-regulation of multiple gene targets (e.g. cyclin D1, A2, c-myc, survivin) and up-regulation of cyclin-dependent kinase inhibitors (e.g. p21, p27) and transcription factors involved in cell cycle arrest (e.g. p53). This has led to the development of GnRH-a analogues as a potential innovative anti-cancer therapy. However, the role of GnRH-a analogues in the treatment of cancer has yet to be fully elucidated. This study aimed to investigate the effects of different GnRH-a analogues on the cell cycle, apoptosis and other mechanisms of gonadotrophin and GnRHR dependent cell death in gonadal and solid tumours. The results of this study will be presented at the conference.

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We have earlier shown that treatment with gonadotropin releasing hormone antagonist blocked adrenocortical tumour progression through gonadotropin suppression in inhibin α/Tag transgenic (TG) mice. Hereby, we investigated the molecular mechanisms underlying the GnRH antagonist (Cetrorelix acetate; GnRH-a) treatment induced potential antitumor effects on gonadal somatic cell and adrenocortical tumours in vivo and in vitro. In vitro treatment with 10 μM GnRH-a significantly decreased cell viability and proliferation of murine K1 (granulosa cell), BLT1 (Leydig cell), Ctx1 (adrenocortical), all three lines originating from inhibin/Tag mice tumours, compared to respective non-treated controls. Flow cytometry analysis revealed a cell cycle arrest at G1 phase in all treated cell lines. We treated in vivo 6-mo-old inhibin/Tag mice bearing gonadal or 6.5-mo-old mice bearing adrenal tumours for 21 days, with either 3 mg/kg b.w./48 h i.p. of GnRH-a or vehicle. Treatments revealed a significant reduction of tumor burden in all types of tumours with GnRH-a treatment vs vehicle treated group. Our results suggest that GnRH-a treatment, besides blocking the release of gonadotropins, may also directly induce tumour cell death.

Disclosure
Singrid Juselius Foundation
Academy of Finland

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EP1135
Genotype-phenotype correlations in a series of patients with von Hippel-Lindau disease in one single tertiary centre
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Background
Von Hippel-Lindau (VHL) disease is an autosomal dominant inherited tumour syndrome with an important phenotypic variability. Genetic testing for VHL is simple and accurate.

Objective
In this study, we investigated the relationships between genotype and phenotype in a series of patients with different VHL gene mutations.

Method
This was a retrospective analysis of the clinical and molecular characteristics of 15 VHL patients followed between 1965 and 2012 at the Cliniques Universitaires Saint-Luc. Patients were divided into two groups in order to investigate possible differences in tumour risk and age of onset. Group 1 included six patients with missense mutations, while group 2 comprised nine patients with nonsense mutations (n = 7), gene deletion (n = 1) or gene insertion (n = 1).

Results
The mean age at onset of symptoms was 20.6 ± 9.1 years. Retinal (27%) and CNS haemangioblastomas (27%) were the most frequent initial presentations. In three cases (20%), the initial presentation was a phaeochromocytoma. The cumulative occurrence was 93% for cerebellar haemangiomas (mean age 28.7 years), 67% for retinal haemangiomas (mean age 25.8 years), 47% for renal cancer (mean age 38.2 years), 53% for phaeochromocytoma (mean age 27.1 years), 53% for multiple pancreatic cysts (mean age 31.8 years) and 33% for pancreatic neuroendocrine tumours (mean age 34.8 years). Eleven different VHL mutations were found: nine mutations in unrelated VHL patients and two mutations in two different kindreds. Patients from group 1 tended to have more frequently a phaeochromocytoma (4/6, 66.7%) than patients from group 2 (2/9, 44.4%), while patients from group 2 tended to have more frequently an endolymphatic sac tumour (3/9, 33.3%) than patients from group 1 (0/6). When we compared prevalence and age of onset of the other types of tumours, we did not find significant differences between the two groups.

Conclusions
In our study there was no significant difference in the phenotype of patients with missense vs nonsense gene alterations.

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EP1136
Clinical characteristics and survival of patients with adrenocortical carcinoma: a single centre experience
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Adrenocortical carcinoma (ACC) is rare malignancy associated with limited treatment options and poor prognosis. The aim of this study is to review clinical characteristics and survival of patients with ACC in single centre. We retrospectively analysed 60 patients (37 female and 23 males) with pathologically confirmed ACC who were treated at our institution between January 2005 and December 2014. Staging was performed according to European Network Study of Adrenal Tumours (ENS/OT) criteria. The median age at diagnosis was 49.0 years (range 14–74), mean tumour size was 11.3 cm (range 3.1–30.3 cm) and median follow-up duration was 34 month (range 3–179). Patients with hormone secreting ACC (43%) mainly presented with isolated Cushings’s (20%), or combined with hyperandrogenism (18%) and 57% of patients had non-functioning tumour. The series included 47% low-stage tumours (three stage I, 25 stage II) and 50% high-stage tumours (no stage III, 30 stage IV). At the time of diagnosis 33% of patients had metastasis. Surgical resection was performed in 90% of patients (73% had adrenalectomy, 15% tumour debulking). At 34 patients the median Weiss score was 6 (range 3–8); proliferation index Ki67 index >10% was in 20/27 patients (median 23.5%, range 2–65%). In our experience, mitotane treatment after surgical resection, and after that date only those with potential residual disease (R1/Rx resection) or with Ki-67 >10%. Since August 2013, plasma mitotane and metabolites levels were measured regularly using HPLC in our institution. Twenty four percent of patients received chemotherapy (EDP 80%, EP 10%, 5FU-DTC-ADM 10%). Median overall survival was 106 months (95%CI 17–194) with 5 year overall survival 53% (76% in stage II, 33% in stage IV). Median disease free survival was estimated 14 months (95%CI 8–20). We presented the overall survival of ACC patients in Serbia, our 10 years experience.

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EP1137
Effects of cyberknife radiotherapy treatment of pituitary adenomas
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Introduction
CyberKnife (CK) is an emerging treatment for pituitary tumours (PT) resistant to other therapies. Patients and methods We report long-term CK effect on endocrine function and tumour volume in 20 PT patients (11M/10F; mean age 58.6 ± 14.4 years). Twelve patients harboured a non functioning adenoma, 2 an ACTH, 5 a GH (one case of TSH co-secretion) and 2 a PRL-secreting PT. Before CK nine patients had normal while 11 presented impaired pituitary function. CK was used as first line treatment in three cases. The mean follow-up period was 21.16 ± 16.35 months (range, 2–90 months). Results MRI demonstrated tumour shrinkage in 50% of patients. Tumour increase was evident only in two cases. Pituitary function impairment occurred in three of the nine patients with previous normal pituitary function who developed isolated deficiency in two cases and multiple deficiencies in 1. Among six patients with previously multiple or isolated hypopituitarism, two became panhypopituitary and one developed a new deficit.

Conclusions
CK treatment for PT is safe and effective, ceasing tumour growth in 90%, and inducing tumour shrinkage in 50% of cases. Nevertheless, impairment of pituitary secretion was demonstrated in 30% of cases with previously intact pituitary function and in 50% of already hypopituitary patients.

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EP1138
Real-time shear wave elastography in the evaluation of parathyroid adenomas
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Real-time shear wave ultrasound elastography (SWE) is a new technique, which evaluates elasticity and stiffness of the different structure.

Aim

To determine the values of the elasticity index (EI) measured by SWE in parathyroid gland adenomas and to compare with those of normal thyroid tissue.

Subjects and methods

We studied 50 cases (F/M = 42/8), ten with primary or tertiary hyperparathyroidism, diagnosed by specific tests, and 40 healthy volunteers. In all the patients with hyperparathyroidism, parathyroid adenomas were detected by using ultrasound and at least another imaging technique. In six cases surgical removal of parathyroid adenomas was performed and the pathological results confirm the diagnosis. For each parathyroid lesion (two or three elastographic determinations were performed and a mean value was calculated and expressed in kilopascals (kPa). In healthy volunteers, thyroid parenchyma was evaluated, by performing three elastographic determinations for each thyroid lobe. A mean value was calculated and expressed in kPa. All the measurements were performed with an Aixplorer system (Supersonic Image, Inc, France), using a linear high-resolution transducer 15–4 MHz.

Results

In ten patients with primary or tertiary hyperparathyroidism, 11 parathyroid adenomas were evaluated by SWE. The mean EI for parathyroid lesions was 9.2 ± 4.8 kPa (4.2–18.2). In healthy volunteers the mean EI was similar in the right and left thyroid 19.9 ± 6.6 kPa vs 19.3 ± 6.6 kPa, P = 0.69, respectively. The statistical analysis indicates that the mean EI assessed by SWE in parathyroid adenomas was significantly lower than in the nearby normal thyroid parenchyma: 9.2 ± 4.8 kPa vs 19.8 ± 6.2 kPa, P < 0.0001.

Conclusion

This new technique can evaluate the EI of parathyroid adenomas, which was significantly lower than EI of normal thyroid parenchyma. This preliminary study indicates that the determination of EI by SWE might be a new method that can help in preoperative localisation of parathyroid adenomas.

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EP1140

Vitamin D receptor and progesterone receptor expression in papillary thyroid carcinoma.

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Background

Vitamin D receptor (VDR) and progesterone receptor (PR) expression have been described before in papillary thyroid carcinoma but data regarding association of this expression with tumour histological characteristics are scarce.

Materials and methods

Formalin-fixed, paraffin-embedded specimens from adult patients with papillary thyroid carcinoma (PTC), who underwent total thyroidectomy from 2009 to September 2012 were retrieved. Data regarding tumour size and aggressiveness were recorded. Real-time quantitative RT-PCR and immunohistochemistry was used to characterise the expression of VDR and PR in thyroid follicular cells of the PTC.

Results

A total of 32 thyroid carcinoma specimens were used in the final analysis. Eighteen cancer specimens (56%) overexpressed VDR and 11 of them (n = 34%) overexpressed PR compared to adjacent normal thyroid tissue. Co-expression of the two receptors was found in seven specimens (22%). Expression of PR but not VDR was significantly associated with the tumour size (r = 0.645, P = 0.007).

Conclusion

VDR is overexpressed in the majority of patients with papillary thyroid carcinoma, compared to normal thyroid tissue. However, the potential role of this receptor in the histological behaviour of PTC remains to be elucidated. Expression of progesterone receptor may be associated with a less favourable prognosis of this tumour type.

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EP1141

Genotype–phenotype analysis in patients with medullary thyroid carcinoma: a single centre experience

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Introduction

Medullary thyroid carcinoma (MTC) is a malignant neoplasm derived from the parafollicular cells of the thyroid gland. Approximately 25% of them are caused by germline mutations of the RET gene, presenting as a part of FMTC, MEN2A or MEN2B syndrome.

Design of the study

We analysed 213 consecutive patients with MTC (142 females, 71 males, age 6–78, mean 45 years), treated in a single centre from 2004 to 2014. Direct DNA sequencing for detection of mutation in coding region of RET exons 5, 8, 10, 11, and 13–16, was performed in all patients.
Results

Mutations in RET protooncogene were found in 89 (41.8%) MTC patients (age 3–72, mean 37.7 years) and their 33 unaffected relatives (age 10–70, mean 40 years), comprising 38 different families. FMTC was diagnosed in 37 (41.6%), MEN2A in 47 (52.8%), MEN2B in 5 (5.6%) of MTC patients. A total of 15 mutations were found. Cys634Ph, Cys634Arg and Val804Met were the most frequent mutations in MTC patients (21.5, 20, and 19.1%, respectively), but the most predominant one among all analyzed patients was Tyr791Phe (30.12% ± 23%). However, only 9 (31%) of these patients were diagnosed with MTC. The rest of the patients were asymptomatic, or with different renal and auditory abnormalities. Polymorphisms of the RET protooncogene were found in 101 (47.4%) of MTC patients. The type or the number of detected polymorphisms did not influence clinical presentation, carcinoid level, or the outcome of the disease.

Conclusion

A higher prevalence of inherited MTC was found in our group of patients than in other studies. The prevalence of different types of mutations among MTC patients is similar as previously reported. However, in contrast to the European studies, an unusually high prevalence of Tyr791Phe mutation was found among our carriers.

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TF33 and TIMP3 – the candidate marker genes for differentiation diagnosis of follicular cell-derived thyroid tumours

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The search for new differentiating biomarkers in follicular-cell derived thyroid tumors (FCDT), especially for the FNAB with undetermined cytology, is an important scientific task. Disturbed expression of tumor suppressor genes plays an important role in thyroid carcinogenesis. In this study we focused on epigenetic mechanism influencing on trefoil factor 3 (TFF3) and tissue inhibitor of metalloproteinases 3 (TIMP3) expression.

Aim of the study

Evaluation of TFF3 and TIMP3 promoter hypermethylation and gene expression as candidate biomarkers in differentiating diagnosis of FCDT neoplasms.

Material

Thyroid neoplasms and matching macroscopically unchanged tissues (control) from 86 patients with preoperative FNAB diagnosis: ‘follicular neoplasm/PTC’. Final diagnosis: FA (n = 9), FTC (n = 35), FTC (n = 9) and NG (n = 33).

Methods

DNA bisulfitest conversion, followed by promoter methylation level evaluation in methylation specific PCR. Methylation Index (MI) calculation. mRNA expression level (RQ) measured by real-time PCR using Low Density Arrays. The results (MI, RQ) were correlated with the clinicopathological features.

Results

TIMP3 MI value correlates with RQ (P = 0.0029) and increase with patients age. TIMP3 MI and RQ are higher in woman vs men (P = 0.0016). TIMP3 MI value was significantly higher in follicular lesions (FTC/FA), than in NG and FTC (P = 0.0049). TIMP3 expression was the highest in FA, the lowest in FTC. RQ values don’t correlate with methylation pattern. TFF3 MI value revealed the opposite correlation to TIMP3 – low MI in FTC/FA. In FTC TFF3 MI correlates with RQ level (P = 0.001). The significant correlations among TIMP3 and TFF3 MI levels and among their expressions were observed (P = 0.0008 for MIs, P = 0.0004 for RQs). In women positive correlation between MIs and RQs for TIMP3 and TFF3 were found (P = 0.0004, P = 0.00 resp.). RQ values regarding pTNM groups reversely correlate with MI for both genes (P > 0).

Conclusions

The increased TIMP3 MI values in FA/FTC, and TFF3 in FTC suggest that can be regarded as promising biomarkers for FCDT distinguishing. Our research indicates that simultaneous analysis of methylation profile and expression level of TIMP3 and TFF3 may be diagnostically useful. Further studies are needed.

Disclosure

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Differentiated thyroid carcinoma arising from or associated with struma ovarii: a report of two cases

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Introduction

Struma ovarii is a rare condition which elicited considerable interest because of its many unique features like its relationship to teratoma and differentiated thyroid cancer. The most common thyroid carcinomas to arise in struma ovarii are papillary and follicular.

Objectives

We describe two patients with differentiated thyroid carcinoma originating from malignant struma ovarii.

Results

Our index patient is a 32-year-old woman with well differentiated follicular carcinoma who developed peritoneal dissemination and appendix tumoral infiltration of a follicular variant of papillary thyroid carcinoma arising from an ovarian teratoma. There was no thyroid carcinoma within thyroid tissue (total thyroidectomy). Whole body scintigraphy (WBS) with therapeutic activity of I-131 (two sessions; cumulated activity: 300 mCi) revealed disseminated pulmonary and bone metastases with a complete response after radioiodine therapy. The second patient is a 49-year-old woman presenting with bone pain revealing bone follicular thyroid carcinoma metastases on biopsy; total
thyroidectomy with lymphadenectomy was performed revealing a follicular thyroid carcinoma T3N1bM1. Two years later, ovariectomy revealed a malignant struma ovarii. Surgical spinal decompression and resection of several vertebral metastases as well as aortic adjuvant radiosurgery therapy (279 MCI-131) were performed. WBS revealed high uptake on cervical lymph node and disseminated pulmonary and skeletal metastases justifying the pursuit of radiosurgical therapy.

Vascular invasion of the thyroid carcinoma within struma ovarii was not identified in any of the cases; however, disseminated metastases were identified. Mechanisms still need to be searched for. At present, treatment for patients with thyroid carcinoma within ovarian malignant struma ovarii comprises resection of the extraovarian tumor tissue with subsequent thyroidectomy followed by radioactive iodine ablation.

Introduction
Testicular Leydig cell tumours (LCTs) are rare stromal tumors often associated with androgen excess. Metastatic malignant LCTs typically show resistance to radiotherapy and cytotoxic chemotherapy, calling for alternative management options. Here we describe our experience with treatment of two patients with metastatic LCTs with the adrenolytic drug Mitotane.

Patients/methods
Case 1: A 51-year-old patient presented with a 6 month history of restlessness, aggressiveness, insomnia, facial plethora and increasing body hair growth, 15 years after successful orchidectomy for malignant LCT. Imaging by computed tomography revealed disseminated metastatic deposits. Biochemical work-up revealed severe androgen excess as the cause of his signs and symptoms, with a plasma testosterone of 93 nmol/l and a 20-fold rise in urinary excretion of active metabolites and substantial inhibition of the conversion of testosterone to oestradiol. Both patients were commenced on palliative chemotherapy with mitotane.

Results
In both cases, introduction of mitotane led to prompt control of the underlying hormonal excess, with a precipitous decrease in circulating testosterone and oestradiol levels, diminution of the excretion rate of all urinary androgen metabolites and substantial inhibition of the conversion of testosterone to dihydrotestosterone, as demonstrated by serial urine steroid profiling by gas chromatography/mass spectrometry. Clinically, this resulted in a rapid alleviation of the debilitating clinical symptomatology of hyperandrogenism. Radiologically, stabilisation of the rapidly progressive disease was documented on follow-up imaging for 6 months in case 1, while partial response was noted in case 2.

Conclusions
Mitotane can be an effective treatment option for patients with functional metastatic LCTs, offering prompt palliation of the distressing symptoms of hormone excess and, in some cases, disease stabilisation.

Disclosure
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EP1146

Patients with multiple endocrine neoplasia type 1 (MEN1) have late progression and long survival despite the presence of disseminated disease: the experience of a referral centre in Greece
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Introduction
Multiple endocrine neoplasia type 1 (MEN1) is a genetic disorder involving mainly parathyroid tumours, pancreatic neuroendocrine neoplasms (pPENs) and pituitary tumours. In the present study we have registered demographic, clinical, imaging, pathological characteristics, therapeutic options, response to treatment and overall outcome of patients with MEN1.

Methods/design
35 patients with MEN1 registered in our database have been studied (14 females, mean age on diagnosis 39 years; range: 15-64), followed during the period 2004–2014. The primary sites, the presence of functional syndrome, and metastatic foci have been registered. TNM system has been used for staging and proliferation index Ki-67 for grading. The therapeutic management and the outcome have been also registered.

Results
24 (68.6%) patients were the index cases. 19 (54.3%) had a positive gene mutation while 5 (14.3%) did not have the mutated gene. 22 (62.9%) patients had a pituitary adenoma and 31 (88.6%) had hyperparathyroidism. All patients but one suffered from pPENs. 11 (32.4%) patients had a functional syndrome. Metastatic liver deposits were found in 6 (17.6%) patients. In the first diagnosis, 21 (61.9%) neoplasms were found in stage 1, 3 (8.5%) in stage 2, 4 (11.9%) in stage 3 and 6 (17.7%) in stage 4. 14 (41.2%) patients had surgical removal of the neoplasms. The other systemic or local therapies that the patients received as monotherapy or in combination as first line treatment are as following: somatostatin analogues (n=5), chemotherapy (n=1), non-pancreatic targeted molecular therapy (n=1), somatostatin analogues and chemotherapy (n=1), and chemotherapy and somatostatin analogues (n=1). The last follow-up of the present analysis 3 (8.6%) patients died of their disease out of the 24 under current follow-up: two with grade 1 pPEN and one grade 2 pPEN.

Conclusion
The present registry implies that the majority of the patients with MEN1 have late progression and long survival despite the presence of disseminated disease, confirming the necessity of specific therapeutic and diagnostic options following the guidelines as well as their management from referral centers under multidisciplinary teams.

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EP1147

Expression of shorter isoforms of retinoblastoma interacting zinc-finger protein in seminomas
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The full-length retinoblastoma interacting zinc-finger protein (RIZ), codified by ten exons, has tumour suppressive and differentiating properties and is known to be a downstream effector in classical oestrogen target tissue. In many normal and malignant tissues alternative splicing isoforms, RIZ1 and RIZ2, frame-shift mutations and/or exon deletions have been found, but their oncogenic role is still debated. Although the presence of RIZ1 in the testis has been described, in gonadal tumours the relative expression of two isoforms, the presence of gene product variants has not been investigated yet. Aim of this study was to evaluate RIZ expression in normal and malignant testis. We analysed five seminomas, four non-seminomas and four control testis tissue samples. RNAs were extracted on frozen samples and RIZ expression measured by semi-quantitative and quantitative Real time RT-PCR using RPS28 as housekeeping gene. In order to identify the presence of different length variants, we analysed the transcripts of the head exon1 of and tail exons 9 and 10.

Results and discussion
RIZ transcript was found in all samples analysed. Moreover, exon 9- transcript levels were higher than C-terminal conventional tail exon 10 level, absent in one seminoma sample. Thus, the balance of head and tail exon transcripts revealed a greater expression of a shorter RIZ gene isoform in seminomas vs non-seminomas and health testis samples. Our data suggest that shorter RIZ isoforms, prevalent in malignant testes, may exert a potential oncogenic and de-differentiating role in male gonad.

Disclosure
This work was supported by PRIN 2008 (grant number 2008SYXTS_005 to AA5).

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**EP1148**

**Succinate dehydrogenase B associated bladder paragangliomas**


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Objective

Succinate dehydrogenase B (SDHB) germline mutations are associated with predominantly extra-adrenal paraganglioma (PGLs) and high rates of metastatic disease. Bladder paragangliomas are a rare form of chromaffin cell tumours arising from the bladder wall. The aim of the study is to highlight the preponderance of bladder paragangliomas associated with SDHB gene mutations.

Design

Retrospective case series.

Patients

Five of eight subjects (62.5%) subjects with bladder paragangliomas found to have SDHB mutations. Subjects were seen at St Bartholomew’s and associated hospitals, between 1989 and 2013.

Measurements

Basic demographics, disease characteristics, genetics, clinical outcomes.

Results

Genetic testing confirmed germline SDHB mutations. Median age at first diagnosis was 24 years (range: 18–68). 60% of patients presented with micturition related symptoms of catecholamine excess. Plasma and/or 24-h urine catecholamines/metanephrines were raised in 4/5 (80%) subjects. A positive family history was apparent in 2/5 (40%). Surgical resection was undertaken in four subjects and one subject awaits surgery. Histopathological or radiological analysis confirmed extension through the lamina propria in 4/5 (80%) subjects. Distant metastatic disease developed in 2/5 (40%) subjects within 4 years of the initial tumour diagnosis. A non-invasive 5-4 mm bladder paraganglioma was identified and excised at an early stage through the SDHB surveillance program. One subject died from metastatic disease 6 years after the initial diagnosis.

Conclusions

The bladder is a ‘hot-spot’ for SDHB associated paragangliomas linked with high rates of invasive disease. Intensive surveillance regimes, with a focus on the bladder can allow early identification and treatment of potentially aggressive disease.

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**EP1149**

**Excision of phaeochromocytoma and paraganglioma involving the great vessels**


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Objective

The aim of the study was to describe the surgical management of phaeochromocytoma and paragangliomas which lie in close proximity to or involve the great vessels including the aorta and vena cava.

Design

Retrospective case-series. Patients: five subjects undergoing surgical excision of either a phaeochromocytoma or paraganglioma involving the great vessels seen at St Bartholomew’s Hospital, UK (2004–2013).

Measurements

Clinical presentation, genetic mutations, tumour location, catecholamine secretion, pre-, intra- and post-operative course.

Results

Of the five subjects (age range 16–60 years), three had thoracic paragangliomas located under the arch of the aorta, one had an abdominal paraganglioma in which preoperative imaging was unable to delineate that the tumour was invading the aorta and one had a massive phaeochromocytoma invading the IVC. Three of the four subjects tested had predisposing germline mutations. All subjects had alpha and beta adrenergic blockade prior to surgery. The thoracic paragangliomas were excised following cardiopulmonary bypass and aortic transection to access the tumours. The abdominal paraganglioma invading the aorta was resected with part of the aorta to clear disease and required insertion of an aortic Dacron graft. The phaeochromocytoma invading the IVC was resected en bloc with the right kidney with a venotomy to extract the tumour nodule invading the IVC. Only one subject experienced an early post-operative complication, which was managed conservatively, and all subjects made a good recovery from surgery.

Conclusion

Excision of phaeochromocytoma and paraganglioma involving the great vessels is high-risk surgery and should be undertaken in a tertiary referral centre within a multidisciplinary setting. Subjects require comprehensive radiological and biochemical assessment. Meticulous pre-operative preparation and appropriate intra- and post-operative back-up are essential. In some cases radiological imaging is unable to resolve the tumour anatomy and extent pre-operatively and direct visualisation of the tumour may be the only way to clarify the surgical strategy. Pre-operative knowledge of the genetic predisposition may influence surgical management.

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**EP1150**

**A one-stop multi-disciplinary VHL clinic: patient benefits and feedback**

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Introduction

Von Hippel-Lindau (VHL) syndrome is a complex multi-organ disorder with significant associated morbidity and mortality. Patients see multiple specialities and have many clinic appointments which can significantly disrupt their lives. In 2012 the St Bartholomew’s VHL multi-disciplinary clinic was set up. It consists of an amalgamated one-stop clinic for patients and their families when all relevant specialities are seen in one sitting. The major aims were to: i) provide a more cohesive service and maximise patient benefit from appointments; ii) consolidate clinical experience and expertise in the management of VHL.

Methods

Analysis of medical records from 2000 until the present day for all VHL patients cared for at St Bartholomew’s Hospital, London. A prospective patient questionnaire was completed by patients attending the clinic.

Results

27 VHL patients (15 male) are under the care of St Bartholomew’s Hospital; 18 (66.7%) attend the multi-disciplinary clinic, 21 completed questionnaires were returned. The mean number of hospital attendances per patient per year was 3.34. This was significantly less after the introduction of the multi-disciplinary clinic (3.59 vs 2.50, P < 0.05). All but two patients attended hospital less frequently after the introduction of the multi-disciplinary clinic. Patient feedback was positive. All respondents thought a one-stop clinic was a good idea and 95% preferred to be seen at the same time as their family. Recurring comments included the benefits of combined consultations and the time saved. The vital role of the specialist nurse was highlighted. Reported downsides were limited and centred on the organisation of the consultation.

Discussion

An amalgamated one-stop multi-disciplinary VHL clinic is practical and reduces hospital appointments whilst being well received by patients. In addition the physical bringing together of all interested parties (both patient and medical) allows for improved communication and truly shared decision making.

**DOI:** 10.1530/endoabs.37.EP1150

**EP1151**

**Progesterone is a potent substance which inhibits the migration of ovarian cancer cells by reducing epithelial-mesenchymal transition via progesterone receptor-dependent pathway**

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Ovarian carcinoma (OC) is the most deadly and leading cause of cancer death occurring in the female reproductive tracts. Several factors involved in ovarian carcinoma remain poorly defined and the therapy for OC is limited. Epidemiological data strongly suggest that endogenous and exogenous steroid hormones may play important roles in ovarian carcinogenesis. One of the primary steroid hormones, progesterone (progesterone), offers protection against ovarian carcinogenesis. We predicted that progesterone would inhibit the migration of...
BG-1 ovarian cancer cells by reducing epithelial-mesenchymal transition (EMT) as well as the growth of cancer cells. First, we investigated the expression of progesterone receptors in ovarian cancer cells with RT-PCR. Next, we determined a proper concentration of progesterone, 17β-estradiol (E2; a positive control), and Mifepristone (anti-progesterone receptor agent) through MTT assay. We confirmed that progesterone reduced the ovarian cancer cell viability in a dose-dependent manner, which was inhibited by Mifepristone. Also, the migration of ovarian cancer cells was reduced by the treatment of progesterone in comparison with negative and positive control groups. Additionally, the alteration of EMT markers such as vimentin was examined at mRNA and protein levels by using reverse-transcription (RT)-PCR and western blot. The expression of Vimentin was reduced in the treatment of progesterone while the expression of its reverse transition marker E-cadherin was increased. These results indicate that progesterone can inhibit the migration of BG-1 ovarian cancer cells by reducing EMT. Further studies using in vivo xenografted mouse models will be needed to predict that progesterone significantly inhibits the growth of ovarian cancer without any virulent effects on the animals. Consequently, the present results represent that progesterone is a potent substance which inhibits the growth of human ovarian cancer cells and metastasis. Therefore, this hormone therapy may be a clinically effective tool for the treatment of human ovarian cancer. (This work was also supported by a grant from the Next-Generation BioGreen 21 Program (NO. PJ009599), Rural Development Administration, Republic of Korea).

Discussion
This work was also supported by a grant from the Next-Generation BioGreen 21 Program (NO. PJ009599), Rural Development Administration, Republic of Korea.

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Clinical Cases – Pituitary/Adrenal

A case of TSH secreting pituitary adenoma with Evans’ syndrome

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Introduction
To the best of our knowledge, there is no case report of Evans’ syndrome associated with TSH secreting pituitary adenoma (TSHoma).

Case report
A 30-year-old woman was admitted to near hospital due to purpura and ecchymoses on her limb and body and epistaxis. A hematologic disease was suspected and she was referred to our hospital. The diagnosis of Evans’ syndrome was made on the bases of idiopathic thrombocytopenic purpura (ITP) and autoimmune haemolytic anaemia (AIHA). Physical examination showed aplegmic features. She had the history of malocclusion and thyroid gland enlargement 4 years prior to admission. Endocrinological tests suggested syndrome of inappropriate secretion of TSH (SITSH) and magnetic resonance imaging (MRI) of the brain demonstrated a pituitary tumor. An oral 75-g glucose tolerance test revealed impaired glucose tolerance, but GH was not suppressed by high serum glucose. Initial studies suggested that this patient had hyperthyroidism due to TSH secreting pituitary adenoma and the adenoma concomitantly secreted GH.

Conclusions
Recently, several cases of Evans’ syndrome associated with hyperthyroidism by autoimmune thyroid disease such as Graves’ disease suggest that these two conditions may have a common immunological background. In our case, hyperthyroidism is due to TSHoma. Thus, it is suggested that thyroid hormone excess itself promote autoimmunity in Evans’ syndrome. The early treatment for hyperthyroidism is necessary in TSHoma because there is the possibility that normalisation of thyroid hormone may prevent the development of Evans’ syndrome.

DOI: 10.1530/endoabs.37.EP1152

A case report of Langerhan cells histiocytosis – the need for a good transition care

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Introduction
Langerhan Cells Histiocytosis (LCH) is a rare heterogeneous idiopathic clinical entity involving clonal proliferation of Langerhan cells that may infiltrate most commonly bone, skin, lymph nodes or lungs. It affects mainly children between 5 and 15 years. The most common endocrine manifestation is diabetes insipida. Clinical case
The authors describe a case of a 19-year-old female patient, admitted in the Transition Follow-up of the Endocrinology Department of Coimbra’s Hospital and Universitary Center. In her past medical history, at the age of 15 months she presented with rash, fever and distended abdomen. Complementary diagnosis exams showed anemia and hepatosplenomegaly and the first bone marrow examination reached the diagnosis of Kala-Azar but the directed treatment did not show clinical improvement. A new bone marrow exam was conducted with a final diagnosis of LCH. After 12 years over the diagnosis, two recurrences and 27 chemotherapy courses she was now referred to Transition Follow-up. On admission she showed no sign of recurrent disease, no anterior-pituitary dysfunction, the maintenance of pituitary stalk thickening at MRI and diabetes insipida, treated with desmopressin.

Discussion
Since it affects mostly children, the majority of published literature about HCL concerns pediatric patients. Our patient reached adulthood and now we face the challenge of planning the future follow-up, concerning the risks of recurrence of the primary disease and the consequences and long-term effects of the treatment of a childhood cancer.

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Recurrent hyponatremia in woman with undiagnosed postpartum pituitary insufficiency

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Introduction
Hyponatremia occurs in 33–69% of women with postpartum pituitary necrosis. The aim of the study was to present a patient in whom recurrent hyponatremia was one of the dominant symptoms of postpartum anterior pituitary hormones deficiency. A case report
55-year-old woman with a diagnosis of Sheehan syndrome established 19 years after the last labor complicated by massive bleeding due to uterine atonia. The first symptoms of pituitary insufficiency were the lack of lactation and secondary amenorrhoea. In addition, the patient complained of weakness, fatigue, psychomotor retardation, depressed mood, dizziness, hypotension including orthostatic hypotension, flushing, loss of appetite, abdominal pain, recurrent episodes of nausea and vomiting, weight loss. She observed dry skin, loss of pubic and axillary hair, loss of eyelashes and eyebrows and recurrent infections of the urogenital system. Over the last few years she was hospitalised for recurrent hyponatremia (Na 115–125 mmol/l) many times. The hormonal measurements were: ACTH = 32.5 pg/ml; cortisol circadian rhythm = 2.6–1.3 μg/dl; daily urine cortisol excretion = 6 μg/day; DHEAS < 3.0 μg/dl (normal range: 25.9–460.2); PRL = 3.5 ng/ml; LH = 1.5 mIU/ml; FSH = 5.03 mIU/ml; estradiol < 12.0 pg/ml; GH < 0.1 ng/ml; IGF-1 = 10 μg/l (normal range: 50–184); fT4 = 6.6 pmol/l; fT3 = 1.1 pmol/l; TSH = 3.26 mIU/l. Ultrasound examination showed the 8.5 ml thyroid gland with normal echogenicity. MRI revealed partial empty sella syndrome with small (7×3 mm), symmetric pituitary with normal morphology of the signal.

Conclusion
Recurrent hyponatremia may be one of the dominant symptoms in the patient with long-lasting and unrecognised pituitary insufficiency after a pathological labour.

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EP1155
Case report: adrenal phaeochromocytoma presenting with ileus, renal vein thrombosis and pulmonary embolism
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Introduction
We report a patient who presented with presumed intestinal obstruction, and was subsequently diagnosed with an adrenal phaeochromocytoma associated with venous thromboembolism. We review the literature and discuss underlying mechanisms for these uncommon manifestations.

Case presentation
A 56-year-old man with background untreated hypertension presented with abdominal distension, vomiting, breathlessness and haemoptysis. Heart rate (HR) was 126/min and blood pressure (BP) 159/95 mmHg at presentation. CT scan of the abdomen revealed dilatation of a long segment of small bowel, with a transition point at the distal jejunum. A heterogeneous 4.6 × 4.5 × 4.9 cm left adrenal mass with associated renal vein thrombosis and left lower lobe segmental pulmonary embolism was noted. Emergent exploratory laparotomy and bowel decompression followed. Intra-operatively, no mechanical cause for intestinal obstruction was identified. Post-operatively, he had uncontrolled hypertension and tachycardia, with BP up to 200/120 mmHg, and HR up to 120–140/min. Urinary catecholamines were ten times above the normal range, confirming the diagnosis of left adrenal phaeochromocytoma. Ga-68 DOTA-TATE PET-CT did not reveal any evidence of metastatic disease. Anticoagulation was started and patient was optimised medically before laparoscopic left adrenalectomy was performed.

Discussion
These uncommon initial manifestations can be explained by a state of catecholamine excess. Ileus occurs due to suppression of gastrointestinal peristalsis. Catecholamines exert a direct effect on primary and secondary haemostasis, and adrenergic infusions have been shown in vivo to increase VIII activity, vWF antigen, IP activity, and platelet activation and aggregation. Both arterial and venous thromboses have been reported in the literature. Overall, these are relatively uncommon and also likely under-reported phenomena in patients with phaeochromocytoma. A greater awareness of these associations will enable clinicians to avoid missing a potentially catastrophic diagnosis.

EP1156
Phaeochromocytoma and hypoglycaemic fits: a case report
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Introduction
Phaeochromocytomas often induce hyperglycaemia. Few cases are reported with hypoglycaemic fits. The mechanism is unknown. Our findings may indicate a mechanism.

The patient
A 37 year old female had a phaeochromocytoma, with typical characteristics: attacks of headache, nausea and sweating. High blood pressures, up to 237/134. Electrocardiogram indicated ischaemia, normal coronary arteries on dynamic CT, normal Echo-Doppler heart examination. HbA1c 6.6%. Fasting glucose 8.8 mmol/l. Plasma metanephrine and normetanephrine, and 24-h-urine adrenaline, noradrenaline and dopamine were increased.

Case report
A 55-year-old lady presented with a 3 weeks history of tiredness, headache, visual disturbances and pyrexia. She had an uncomplicated trans-sphenoidal adenomectomy surgery for TSH and GH secreting adenoma 6 months previously. She had evidence of pan hypopituitarism with a peak cortisol response of a short synacthen test of 280 nmol/l at 30 min, adrenocorticotropic hormone level of <5 ng/l, low gonadotrophin, low free T3 and inappropriately normal thyroid-stimulating hormone level. A lumbar puncture was done showing evidence of viral meningitis. Initial magnetic resonance imaging (MRI) of pituitary showed evidence of likely recurrence of her pituitary adenoma. However, due to the presence of pyrexia and viral meningitis a MRI pituitary with contrast was subsequently performed. This confirmed evidence of multiculated pituitary abscess with optic chiasm compression. She was commenced on intravenous hydrocortisone, thyroxine, intravenous acyclovir and antibiotics and transferred to a neurosurgical centre for drainage of the abscess.

Discussion
Normally alphaadrenergic stimulation of β-cells inhibits, while βadrenergic stimulation increases insulin secretion. Three findings may indicate that her catecholamines have caused abnormal βadrenergic stimulation of insulin release: persistence of hypoglycemic fits after alphablockade; unusual response to the small βblocker dose, suggesting an abnormal βadrenergic tone; no fits postoperatively.

Conclusion
Our phaeochromocytoma patient had the rare variant with hypoglycemic fits. They were hyperinsulinemic, possibly caused by excessive βadrenergic stimulation of insulin secretion.

DOI: 10.1530/endoabs.37.EP1156

EP1157
An uncommon complication of post trans-sphenoidal surgery for pituitary adenoma
Hiang Leng Tan & Kurien John
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Introduction
The commonest complications post trans-sphenoidal surgery is diabetes insipidus and the development of anterior pituitary hormone deficiencies. Other complications include meningitis, CSF leak, visual deterioration, haemorrhages and transient hypotension. We present a case of pituitary abscess 6 months post pituitary surgery who presented with viral meningitis and panhypopituitarism.

Case report
A 55-year-old lady presented with a 3 weeks history of tiredness, headache, visual disturbances and pyrexia. She had an uncomplicated trans-sphenoidal adenomectomy surgery for TSH and GH secreting adenoma 6 months previously. She had evidence of pan hypopituitarism with a peak cortisol response of a short synacthen test of 280 nmol/l at 30 min, adrenocorticotropic hormone level of <5 ng/l, low gonadotrophin, low free T3 and inappropriately normal thyroid-stimulating hormone level. A lumbar puncture was done showing evidence of viral meningitis. Initial magnetic resonance imaging (MRI) of pituitary showed evidence of likely recurrence of her pituitary adenoma. However, due to the presence of pyrexia and viral meningitis a MRI pituitary with contrast was subsequently performed. This confirmed evidence of multiculated pituitary abscess with optic chiasm compression. She was commenced on intravenous hydrocortisone, thyroxine, intravenous acyclovir and antibiotics and transferred to a neurosurgical centre for drainage of the abscess.

Discussion
 Normally alphaadrenergic stimulation of β-cells inhibits, while βadrenergic stimulation increases insulin secretion. Three findings may indicate that her catecholamines have caused abnormal βadrenergic stimulation of insulin release: persistence of hypoglycemic fits after alphablockade; unusual response to the small βblocker dose, suggesting an abnormal βadrenergic tone; no fits postoperatively.

Conclusion
Our phaeochromocytoma patient had the rare variant with hypoglycemic fits. They were hyperinsulinemic, possibly caused by excessive βadrenergic stimulation of insulin secretion.

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EP1158
Polyglandular autoimmune syndrome type 2 (Schmidt’s syndrome)
Paiza Qari & King Abdulaziz, Jeddah, Saudi Arabia.

A 58-year-old Saudi female presented with fatigue, dizziness and generalised skin hyperpigmentation. She was diagnosed as Hashimoto’s hypothyroidism. She was diagnosed recently to be diabetic and her blood sugar was controlled with insulin. She reached menopause at the age of 36 years.

Lab results

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT4</td>
<td>15 pmol/l</td>
</tr>
<tr>
<td>TSH</td>
<td>36 ulU/l</td>
</tr>
<tr>
<td>Antithyroglobulin AB</td>
<td>1:1600</td>
</tr>
<tr>
<td>Cortisol at 8.00</td>
<td>3.6 µg/dl</td>
</tr>
<tr>
<td>ACTH</td>
<td>850 pg/mL</td>
</tr>
</tbody>
</table>

BPs 90/60 mmHg sitting and 70/50 mmHg standing. Generalised hyperpigmentation of the skin. Diagnosis is polyglandular autoimmune syndrome type 2 (Schmidt’s syndrome) was made on the basis of concomitant Hashimoto’s hypothyroidism; premature ovarian failure; Addison’s disease; IDDM.

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EP1159
Sellar plasmacytoma masquerading as pituitary macroadenoma – a case report
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A 49-year-old male presenting with acute onset strabismus on left lateral gaze was admitted to the Endocrinology Department. The CT scan showed a 35×40×25 mm tumour mass, presumed to be a pituitary macroadenoma, in the sellar region which extended into the sphenoidal sinus, clivus, posterior ethmoidal cells, petrous part of the temporal bone and towards the nasopharynx. A MR scan of the head also revealed that the mass displaced the anterior pituitary gland and the infundibulum upwards. The MRI result was not typical for pituitary macroadenoma and raised the possibility of another tumour. A biopsy was performed and a specimen of the sphenoidal sinus mass was obtained. The histological examination revealed that the tumor was a moderately differentiated plasmacytoma with restriction to kappa light chains and a serum proteinogram showed a disturbance in the k/λ ratio with a raise in the free k light chains. A radiographic skeletal survey showed a suspect lesion of the 8th thoracic vertebra. Reference Virology Laboratory for IFA and immunoblot test which revealed hantavirus IgM and IgG antibodies. Hantavirus seropositivity was determined by two tests. Magnetic resonance imaging revealed sella and suprasellar mass (22×23×30 mm) with evidence of acute hemorrhage and diagnosed as PA. The patient underwent transsphenoidal surgery. Histopathological examination showed signs of recent bleeding. 12 months after surgery, the patient with persistent hyperprolactinemia is given steroid, l-thyroxine and testosterone treatment. Thus, physicians should suspect PA in a patient with hemorrhagic fever who develops a rapid onset of severe headache, even in a patient without a known pituitary adenoma.

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EP1160
Pituitary apoplexy case caused by Hanta virus infection
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Pituitary apoplexy (PA) is a rare but life-threatening medical emergency. Common predisposing factors include closed head trauma, blood pressure alterations, history of pituitary irradiation, cardiac surgery, anticoagulation, treatment with dopamine agonists, pituitary stimulation testing, and pregnancy. Hantaviruses belonging to the Bunyaviridae family are a group of rodent- or insectivore-borne single-strand ribonucleic acid (RNA) viruses. In humans, hantaviruses can cause haemorrhagic fever with renal syndrome or cardiopulmonary syndrome. About one third of the patients may occur bleeding in the brain, conjunctiva or gastrointestinal tract. Pituitary hemorrhage due to pituitary insufficiency have also been reported. We report the case of a patient, who the 62-years-old man was admitted to the emergency department with complaints of fever, severe headache and confusion. There was no disease in his history. He had not taken any medication or had bleeding disorder prior to this presentation. Leukopenia, thrombocytopenia, elevated liver enzymes and creatinine and panhypopituitarism was detected in laboratory investigations at intensive care. The patient underwent hemodialisis and stress-dose methylprednisolone was taken. The patient's pituitary-adrenal axis also became insufficient. Plasmacytoma in the treatment with bortezomib and dexamethasone as well as radiotherapy, the patient’s pituitary-adrenal axis also became insufficient. Plasmacytoma in the infundibulum upwards. The MRI result was not typical for pituitary macroadenoma and raised the possibility of another tumour. A biopsy was performed and a specimen of the sphenoidal sinus mass was obtained. The histological examination revealed that the tumor was a moderately differentiated plasmacytoma with restriction to kappa light chains and a serum proteinogram showed a disturbance in the k/λ ratio with a raise in the free k light chains. A radiographic skeletal survey showed a suspect lesion of the 8th thoracic vertebra. Reference Virology Laboratory for IFA and immunoblot test which revealed hantavirus IgM and IgG antibodies. Hantavirus seropositivity was determined by two tests. Magnetic resonance imaging revealed sella and suprasellar mass (22×23×30 mm) with evidence of acute hemorrhage and diagnosed as PA. The patient underwent transsphenoidal surgery. Histopathological examination showed signs of recent bleeding. 12 months after surgery, the patient with persistent hyperprolactinemia is given steroid, l-thyroxine and testosterone treatment. Thus, physicians should suspect PA in a patient with hemorrhagic fever who develops a rapid onset of severe headache, even in a patient without a known pituitary adenoma.

DOI: 10.1530/endoabs.37.EP1159

EP1161
Pasireotide - the last treatment option in Cushing’s disease - case report
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Introduction
The most common cause of Cushing’s disease is ACTH secreting tumours of the pituitary gland. It is associated with high morbidity and mortality. Pasireotide, a potential therapy, has a unique, broad somatostatin-receptor–binding profile, with high binding affinity for somatostatin-receptor subtype 5.

Case report
We present the a 40-years-old man diagnosed in 2005 with Cushing’s Disease for which a left adrenalectomy was performed (pathology report: diffuse and nodular adenomatous hyperplasia). In January 2006 gave the presence of hypercortisolism and the adenomatous hyperplasia in the right adrenal gland (49/29 mm), surgery was performed on this location also. After surgery, evolution was not good, the signs and symptoms of Cushing’s Disease persisted, the urinary cortisol levels were very high and for this Ketoconazole treatment (200 mg x 3 per day) was initiated. Another surgery was performed on the left adrenal gland (CT showing a 1.5 cm nodule). Until 2008 the blood and urinary cortisol levels remain upper limit under Ketoconazole therapy, High ACTH and pituitary microadenoma require transsphenoidal surgery to practiced and which has proved to be ineffective. Another surgery is required which manages to normalize the ACTH and cortisol levels until 2012. Re-growth of ACTH requires begun the treatment with corticosteroid 4 mg (6/4 cp per day). When admitting of July 2014 ACTH and cortisol values are maintained above the limit: ACTH = 177 pg/ml, Cortisol = 15 μg/dl, UFC = 1753 nmol per day, and the MRI showing the pituitary microadenoma. We decide to start the treatment with Pasireotide (0.6 mg x2 per day) with a 2 months follow up (in October) when ACTH and cortisol have been normalized.

Conclusions
In our patient’s case Pasireotide was the last and the only option, because the other proved inefficient in time. The significant decrease in cortisol levels in patients with Cushing’s disease who received pasireotide supports its potential use as a targeted treatment for corticotropin-secreting pituitary adenomas. DOI: 10.1530/endoabs.37.EP1160

EP1162
Lump it or leave it & bilateral adrenal macronodular hyperplasia: Case report and clinical insights
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Clinical case
MG was a 57-year-old female when first referred to endocrinology for investigation of adrenal incidentaloma. Relevant medical history included poorly controlled hypertension on two agents, dyslipidemia and history of minimal trauma fracture. Baseline labs (including 24 h urine collection) were unremarkable as was clinical examination (except hypertension). Cortisol levels on two 1 mg Dexamethasone suppression tests failed to suppress. Dedicated CT adrenal study showed bilateral adrenal hyperplasia: left gland was largest. A diagnosis of bilateral adrenal macronodular hyperplasia with subclinical Cushing’s syndrome was made. Further investigations showed high grade osteoporosis and normal results for aberrant receptors (TRH, GnRH, mixed meal and postural changes) and Short Synacthen test with 17-OH-P levels. Adrenal vein sampling was

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performed that confirmed diagnosis. Immediate progress included continued hypertension now needing three agents; moderate weight gain and new minimal trauma vertebral fracture. Following discussion with MG regarding diagnosis and its associated complications (metabolic syndrome and osteoporosis), the treatment options of medical management of complications and monitoring vs medical treatment vs surgery, she elected for medical management and monitoring. Follow-up CT adrenal studies showed interval increasing size in both glands, persistent osteoporosis despite bisphosphonate treatment and moderate weight gain. Hypertension and dyslipidaemia were controlled. 4 years following initial diagnosis, MG elected for surgery and successfully underwent a laparoscopic posterior extra-peritoneal left adrenalectomy. Post-operatively she does not require glucocorticoid therapy and reduced dosages of hypertensive medications. She continues to be followed up by endocrinology.

Discussion

This case highlights the challenges in recognising and managing bilateral adrenal macronodular hyperplasia and its complications. The natural history of the condition and role of investigations including for CAH and receptor testing, the value of adrenal venous sampling, imaging options and medical and surgical treatment options will all be explored.

DOI: 10.1530/endoabs.37.EP1162

EP1163

Clinical nonsecreting pituitary macroadenoma managed by cabergoline: anybody, anytime?

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Introduction

Therapeutic management of clinical nonsecreting pituitary adenomas with ophthalmological manifestations is certainly limited to surgery unless IHC from previous intervention could bring up new data.

Case report

A 16-year-old patient was admitted in February 2014 in our Endocrinology Department for short stature (–3.5 s.d.), in the context of an iatrogenic pituitary insufficiency. 7 months before, he had been diagnosed with pituitary macroadenoma of 36/24/30 mm which invaded the sphenoidal sinus anteriorly and had a contact with the optic chiasm, causing left cecity. He undergone frontal adenomectomy, with a ACTH and TSH deficit that were currently substituted. Clinically: short stature (149.9 cm, –3.5 DS), underweight, BP=95/60 mm/Hg, Tanner stage P5G3, left temporal hemianopsia. Biologically: low lGFI (–3 DS), maximum stimulated GH 0.226 during insulin induced hypoglycemia, normal testosterone, LH=1.9, normal ACTH, TSH and prolactin. The pituitary MRI showed an adenoma of 3.2/3.6/3.4 cm, the hand X-ray showed a bone age similar to the chronological age, with open growth cartilages and the visual field a left temporal hemianopsia. According to the family’s choice not to reoperate, we decided to start the treatment with cabergoline as the adenoma had IHC prolactin, LH, FSH, TSH and GH staining. We started with a dose of 1 mg/week and progressively increased the dosage up to 3 mg/week, with visual field evaluation every 1–2 months and MRI after 6 months. The left hemianopsia improved and was stable for 3–5 months, the MRI showed no evolution, but after 6 months the patient developed right hemianopsia and nausea, so surgery was recommended.

Conclusion

Cabergoline treatment of nonsecreting tumors with IHC staining for D2 receptors is a new strategy with optimist results in recent studies; however, close monitoring is mandatory during the treatment in order to identify non-responders and assure an individualised therapeutic decision.

DOI: 10.1530/endoabs.37.EP1163

EP1164

Catecholamine-induced cardiomyopathy: pitfalls in diagnosis and management

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Introduction

Cardiomyopathy as the initial presentation of pheochromocytoma (PCA) is uncommon. Diagnostic workup and perioperative management may be challenging within this context. We report three cases of PCA presenting with cardiomyopathy to illustrate the pitfalls in diagnosis and management. None of the patients had typical adrenergic symptoms of catecholamine excess and all patients were well established on beta-blockers on presentation. All three patients had an adrenectomy and a PCA was confirmed on histology.

Cases: Patient A: A normotensive 56-year-old male with dilated cardiomyopathy, was found to have an incidental longstanding right adrenal nodule. Plasma and urine metadrenaline levels were raised during compensated heart failure and improved with treatment. However, a subsequent increase in metadrenaline levels was noted despite clinical and echocardiographic improvement of cardiac function. MBG and Octreotide scans were both negative but CT of the right adrenal with wash out studies showed indeterminate characteristics. Patient B: A 66-year-old male was referred with a right adrenal mass. Previous investigations revealed severe left ventricular impairment and non-flow limiting coronary disease. Plasma and urine metadrenaline were raised and asymmetrical adrenal uptake was noted on an MBG scan. Patient C: A 61-year-old female with type 1 Neurofibromatosis presented with Takotsubo cardiomyopathy. Fractionated metadrenaline levels were raised and a MBG avid left adrenal lesion, corresponding to a left adrenal mass on CT scan, was found.

Conclusions

Interpretation of fractionated metadrenaline levels in the context of established cardiomyopathy is difficult as cardiac failure of any aetiology generates an adrenergic response. Screening all patients with idiopathic cardiomyopathy for catecholamine excess is highly likely to generate false positive results. However, a high index of suspicion should prompt further investigations of patients with idiopathic cardiomyopathy for occult an PCA. Peer reviewed guidelines are required to guide the investigation and management of suspected catecholamine-induced cardiomyopathy.

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EP1165

Histiocytosis, a rare cause of hypopituitarism. Langerhans cell histiocytosis and Erdheim–Chester disease, two case reports of pituitary deficiency

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Introduction

Langerhans cell histiocytosis (LCH) is a rare disease with incidence of 1–2 adults per million/year. Pituitary function is affected in 30% of cases presenting almost always with diabetes insipidus. Other deficiencies such as GH, FSH+LH, TSH and ACTH follow. Erdheim–Chester disease is a rare Non-LCH described in several hundreds of cases in the world so far, with the pituitary function involvement in similar frequency as in LCH.

Case 1

A 36-year-old man has been treated for diabetes insipidus, central hypogonadism and severe GH deficiency of unknown origin since 2006. In 2014 MRI showed a hypothalamic lesion with involvement of pituitary stalk and other small lesions around IV. ventricle. PET/CT revealed maxillary and mandible lesions with adjacent soft and lymphatic tissue involvement. A biopsy from recently discovered scalp lesions, previously described as [foliculitis capitis] in the scalp, proved LCH. Otitis externa was another manifestation of LCH.

Case 2

A 42-year-old man has been diagnosed with isolated diabetes insipidus. MRI showed an infiltration of hypothalamus and pituitary stalk. Biopsy from suspicious papule on the arm did not reveal LCH as CD1a and S100 stains were negative. Additional PET/CT scan showed a multifocal bone involvement. The clavicle biopsy was in agreement with the skin papule biopsy and diagnosed an Erdheim–Chester disease.

Conclusions

Histiocytosis should be considered in case of a diabetes insipidus with/without other pituitary deficiency and hypothalamic lesion. Other organs such as bones, skin, lungs, lymphatic tissue and others can also be involved and PET-CT scan can reveal it. A biopsy from the extrapituitary lesion can lead to the diagnosis.

DOI: 10.1530/endoabs.37.EP1165
Bone densitometry: glucose tolerance test showed unsuppressed GH on glucose load (nadir GH 15.1 pg/ml (0.3–4.7), FT4: 6.0 pmol/l (9.5–21.5); FT3: 2.7 pmol/l (3.5–6.5). Prolactin was hormone binding globulin 26 nmol/l (15–48). Alpha sub-unit was also elevated (130–180) with borderline high haematocrit of 0.51 l/l (0.40–0.50). Sex hormone optic chiasma. His blood results showed high normal haemoglobin of 180 g/l and mildly high at 982 μg/dl, serum cortisol (after 1 mg overnight dexamethasone suppression) 27 μg/dl confirmed by MSCT scan. Active phaeochromocytoma was excluded by normal urinary catecholamines. Endocrine evaluations revealed normal midnight cortisol, with post 1mg-DST cortisol suppression and normal basal ACTH. PRA and Aldosterone were in normal range with normal ALD/PRA ratio. According to MSCT tumour had some malignant neoplastic features. Surgery was performed. Intraoperative findings showed adrenal tumour about 5 cm sizes without signs of local infiltration or lymphadenopathy. Tumour was completely removed with adrenalrenoma. Pathophysiology showed cavernous and partially capillary hemangiomia with hyperplasia of the rest of adrenal gland. 6 months later patient was restented and results show normal function of the left adrenal gland. Most of adrenal cavernous hemangiomia was non-functional and surgical removal was the right choice of therapy. They should be also the part of differential diagnosis of adrenal incidentaloma.

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EP1168
Adrenal cavernous hemangiomia
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Adrenal hemangioma is a rare adrenal tumour usually presented as incidental finding in asymptomatic patients. Due to its radiographic features sometimes it’s difficult to differentiate them from other malignant lesions. We present a 55-years-old man admitted to our department with adrenal incidentaloma size 5×4 cm confirmed by MSCT scan. Active phaeochromocytoma was excluded by normal urinary catecholamines. Endocrine evaluations revealed normal midnight cortisol, with post 1mg-DST cortisol suppression and normal basal ACTH. PRA and Aldosterone were in normal range with normal ALD/PRA ratio. According to MSCT tumour had some malignant neoplastic features. Surgery was performed. Intraoperative findings showed adrenal tumour about 5 cm sizes without signs of local infiltration or lymphadenopathy. Tumour was completely removed with adrenalrenoma. Pathophysiology showed cavernous and partially capillary hemangiomia with hyperplasia of the rest of adrenal gland. 6 months later patient was restented and results show normal function of the left adrenal gland. Most of adrenal cavernous hemangiomia was non-functional and surgical removal was the right choice of therapy. They should be also the part of differential diagnosis of adrenal incidentaloma.

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EP1167
Gonadotrophin secreting pituitary adenoma with hypersecretion of testosterone and testicular enlargement
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Gonadotroph pituitary adenomas are common but majority of them are classified as non-functional as they do not lead to features of hormonal excess. Functional gonadotroph adenomas are rare and there are only few small series or individual case reports about these. Case report: 45-year-old gentleman presented with headaches, progressive visual field loss and enlarged testes (about 90% of all cases. Primary empty sella syndrome (ESS) results from herniation of arachnoid mater into the pituitary fossa. Since it has been demonstrated that the small anterior pituitary size reflects loss of neurotrophin expression in the hypothalamus, leading to reduced GHRH, pituitary GH and IGF1 production, we agree that IGF1 and GH increased in our patient can be attributed to loss of neurotrophin expression and consequent reduced GHRH and subsequent increased pituitary GH and IGF1 production. We also speculate that growth hormone and IGF1 may have an impact on GH and IGF1 production, we agree that IGF1 and GH increased in our patient can be associated with hypopituitarism. GH deficiency is more common in patients with NF. Since this rare case presents a young patient with NF, ESS and an uncommon excess of GH, careful evaluation, diagnosis and follow-up appears to be essential.

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therapy 6 months after the surgery with progressive reduction. She is waiting to see clinical and analytical evolution to suspend such treatment.

Conclusion
Adrenocortical oncocytoma, although extremely rare, should be considered in the differential diagnosis in adrenal masses. They are usually non-functional and benign but few cases are functioning tumours and may cause Cushing’s syndrome. To make a correct diagnosis, biochemical, clinical and histological features must be analysed together.

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EP1170
Adrenal insufficiency revealing pseudotumoral surrénale tuberculosis
Samir Ait Abderahmame, Meriem Bensalah, Yamina Aribi, Lila Brakni, Samia OuldKablia & Zahra Kemali
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Adrenal tuberculosis was first described by Thomas Addison in 1855. Isolated adrenal tuberculosis is rare and between represents 1–2% of the aetologies of adrenal masses called incidentalomas. We report the case of a related Addison’s disease is a progressive adrenal tuberculosis which could benefit from exploration and a tomography monitoring on anti tuberculosis treatment. Patient aged 35 years presented himself to medical emergency with clinical surgical nickname, the diagnosis of adrenal insufficiency decompensation was made. Our patient underwent adequate replacement therapy, with correction of electrolyte disturbances. The aetiological investigation concluded in adrenal tuberculosis on the basis of arguments. History of pulmonary tuberculosis treated, melanoderma gradual onset, progressive weight encrypted fall has 16 kg in 3 years, TA figures tend to decline, Malaise hypoglycemic with difficulty fasting month of Ramadan. TST positive tuberculin 25 mm.La chest X-ray shows pulmonary tuberculosis effects and abdominal CT shows bilateral adrenal hypotrophy presence of multiple nodules that larger situated right 21 mm major axis. After a treatment based TB established for 6 months, a radiological objective control complete disappearage of radiological lesions surrenalen. Un base cortical is collapsed income 89 ng/l. In light of this observation we update on this rare disease. Adrenal tuberculosis can be discovered on the occasion of the setting evidence of adrenal mass was the initial phase of bacillary disease, there adrenal hypotrophy before the appearance hormonal insufficiency.

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EP1171
Three cases of successful pregnancy outcomes after different methods of therapy in women of acromegaly apart from remission of the disease
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Reports of pregnancy in acromegalic women are uncommon.

Case 1: Patient K., 25-year-old., 01/04/2008 – transphenoidal adenomectomy in connection with active acromegaly (GH/OGTT – 47.2–64.0–38.0–29.6–28.7 ng/ml; macroadenoma 19x14x12 mm with compression of optic chiasm). Postoperative remission of the disease, recovery of menstrual function without additional therapy. At the end of August 2008 the patient became pregnant, in the beginning of June 2009 – childbirth. After 6 months – the second successful pregnancy. The both children are wellbeing till now.

Case 2: Patient Yas., 32-year-old., 24/02/2005 – partial transsphenoidal adenomectomy without remission due to spreading macroadenoma into left cavernous sinus around ICA. After surgery patient received additional therapy with SSA (Somatulin 30 mg twice a week till 2006, then Sandostatin LAR 40 mg in combination with cabergoline 1 mg a week) without cure of the disease: IGF1 with SSA (Somatulin 30 mg twice a week till 2006, then Sandostatin LAR 40 mg in combination with cabergoline 1 mg a week) without cure of the disease: IGF1 28.7 ng/ml; macroadenoma 19 mm with compression of optic chiasm). After surgery patient received additional therapy with SSA (Somatulin 30 mg twice a week till 2006, then Sandostatin LAR 40 mg in combination with cabergoline 1 mg a week) without cure of the disease: IGF1 28.7 ng/ml; macroadenoma 19 mm with compression of optic chiasm). In the beginning of March 2010 – childbirth. The both children are wellbeing till now. After childbirth SSA therapy have been initiated.

Case 3: Patient P., 30-year-old. Primary infertility during 10 years. Two-fold partial transphenoidal adenomectomy (in 1998 and 2001) without remission due to macroadenoma with supra-infra-latero-cellar extension. In 2002 – conventional gamma-therapy, 50 G. In one year after radiotherapy – active acromegaly (GH-25 ng/ml; IGF1 – 690 ng/ml) and spontaneous pregnancy with successful outcome. The boy is wellbeing till now. After childbirth SSA therapy have been initiated.

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EP1172
An unusual cause of central diabetes insipidus
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Introduction
In 30–50% of cases central diabetes insipidus (CDI) is idiopathic. Other causes include tumours, pituitary surgery, cranial trauma or infiltrative diseases. Long-term medical follow-up is crucial given that idiopathic CDI can be the earliest sign of an evolving process (inflammatory or tumoural).

Case report
We report the case of a 23-year-old woman who presented with isolated polydipsia and polyuria. The diagnosis of isolated CDI was established. Magnetic resonance imaging of the pituitary gland showed thickening of the pituitary stalk and loss of normal hyperintense signal of the posterior pituitary on T1-weighted images. A 18F-FDG PET/CT revealed a tumor-like lesion in the right kidney which was confirmed by a renal contrast-enhanced ultrasonography (CEUS). Granulomatous with polyangitis (GPA) was suspected on the basis of associated maxillary sinus hypermetabolism on PET/CT and plasmatic anti-MPO ANCA positivity. Strikingly, urinalysis and renal function were normal. Furthermore sinus biopsy revealed no granulomatous inflammation. Ultrasound control performed six months later showed that the right renal mass had doubled in diameter and demonstrated new lesions in the left kidney. Renal function and urinary sediment still remained normal. Finally, US-guided biopsy of the right renal tumour revealed granulomatous inflammation consistent with the diagnosis of GPA.

Conclusions
GPA is an ANCA-associated systemic vasculitis which classically affects the upper and lower respiratory tracts and kidneys. Pituitary involvement is very rare. Renal impairment is usually characterised by glomerulonephritis with hematuria and/or proteinuria leading to progressive renal failure. Only 16 cases of GPA with renal pseudotumours have been reported. To our knowledge this is the first case combining CDI and subsequent bilateral renal tumours in the setting of GPA. This affection should be considered in the differential diagnosis of CDI. Early diagnosis and initiation of treatment could minimize the risk of irreversible pituitary function loss.

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EP1173
Longest survival with central diabetes insipidus; more than 30 years without and 25 years with desmopressin treatment
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Introduction
Diabetes insipidus (DI) is a disease characterized by excessive thirst, polydipsia and excess diluted urine caused by insufficiency of antidiuretic hormone or renal resistance to its effect. Although it is generally a benign condition, severe hypernatremia and hypertonicity may cause death if water loss is not compensated.

Case report
A 72-years-old man admitted to our clinic for routine control. In medical history, he told that when he was about 9 years, polyuria and polydipsia had started and he was diagnosed to have DI when he was 17 years old in 1959. At that time, he was told to drink water as much as possible since there was not any drug available in our country. He had been drinking about 15–16 l of water in those years. About 25 years ago, desmopressin became available in our country and the patient had started desmopressin treatment. From then on, polyuria and polydipsia had
resolved and the dosage was progressively increased to 3×20 mg/day. He did not have any other chronic disease except hypertension regulated with amlodipin. In laboratory examination, serum sodium was 141 mmo/l, potassium 4.1 mmo/l, urinary density 1014, serum osmolality 291 mOsm/l and urine osmolality 486 mOsm/kg water. His anterior hypophyseal hormones were normal and magnetic resonance imaging revealed a normal hypophyseal gland with a height of 4.3 mm.

Conclusion

To our knowledge, the longest follow-up time reported in studies or case reports including patients with central DI in the literature does not extend beyond 30 years. Our patient has the longest survival of more than 55 years of which 30 years passed without any medical treatment. This is supportive for the fact that loss of urine can be compensated and water balance can be maintained as long as thirst mechanisms work and water intake is provided.

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EP1174

Positive MIBG scan in a patient with adrenal failure secondary to lymphoma: a coexistent paraganglioma or false positive involvement?

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Introduction

We report stage IV B cell lymphoma in a patient presenting with adrenal failure and an intraabdominal mass which imaging techniques were suggestive for paraganglioma.

Case report

A 71-years-old woman admitted to our emergency clinic with severe fatigue and stupor. She was diagnosed to have primary adrenal failure since serum ACTH was 229 pg/ml and cortisol response to 250 μg co-syntropin was 6.17 μg/dl. In abdominal MRI, bilateral adrenal enlargement and a 35×31 mm paraaortic lesion consistent with paraganglioma (heterogenous, markedly increased contrast uptake, milimetric cystic foci) were detected. 123I-MIBG showed diffuse uptake in the lesion. 24 h urine metanephrine, normetanephrine and VMA levels were moderately increased. She did not have persistent or intermittent hypertension.

During investigation for the cause of adrenal failure, multiple mediastinal and hilar lymph nodes (24×7 mm the biggest) were observed in thoracal CT and a lymph nodal mass consistent with paraganglioma (heterogenous, marked increase in contrast uptake, milimetric cystic foci) was detected. 123I-MIBG showed diffuse uptake in the lesion. 24 h urine metanephrine, normetanephrine and VMA levels were moderately increased. She did not have persistent or intermittent hypertension. In the lesion, 24 h urine metanephrine, normetanephrine and VMA levels were moderately increased. She did not have persistent or intermittent hypertension. In the lesion, 24 h urine metanephrine, normetanephrine and VMA levels were moderately increased. She did not have persistent or intermittent hypertension. In the lesion, 24 h urine metanephrine, normetanephrine and VMA levels were moderately increased. She did not have persistent or intermittent hypertension. In the lesion, 24 h urine metanephrine, normetanephrine and VMA levels were moderately increased. She did not have persistent or intermittent hypertension. In the lesion, 24 h urine metanephrine, normetanephrine and VMA levels were moderately increased. She did not have persistent or intermittent hypertension.

Conclusions

To our knowledge, coexistent paraganglioma and lymphoma was not reported in the literature previously. However, since we did not have histopathological confirmation, false positive MIBG uptake secondary to lymphoma could not be excluded. Although 123I-MIBG is known to have a sensitivity of 77–90% and specificity of 88–99% for localizing paragangliomas, lymphoma might be one of the causes of false positivity in addition to some other rare causes such as angiomylipoma.

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EP1175

Synacthen induced phaeochromocytoma crisis, an unusual presentation

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A 75 male was referred to endocrine service with incidental pituitary macroadenoma measuring 4.2×3.1×3.3 cm noted on MRI-C-Spine done for anklyosing spondylitis with Atlanto-axial joint instability. He had reduced secondary sexual characteristics and left quadrantanopsia. Endocrine studies confirmed thryostrof and gonadotroph failure but normal lactotroph and HPA axis. He underwent trans-sphenoidal tumour resection followed by external beam radiation due to tumour residuum. His quadrantanopsia resolved completely and he was started on annual pituitary assessment. 2 years later he developed palpitations and collapsed following Synacthen injection for short Synacthen test (SST). He made full recovery and initial work up demonstrated no clear cause. A repeat SST 6 month later resulted in palpitations and near collapse. An evolving history of frequent episodes of palpitations and sweating accompanied by headache over the previous months was noted, which raised suspicion of phaeochromocytoma. Plasma metanephrines were then marginally elevated (metadrenaline 1140 (80–510) pmol/l, normetadrenaline 3833 (120–1180) pmol/l). This rose further in the following 3 months (metadrenaline 3008 pmol/l, normetadrenaline 5387 pmol/l) and 24 urine analysis demonstrated raised indices to creatinine (metadrenaline/creatinine 1.14 (0–0.3) umol/mmol, normetadrenaline/creatinin 0.76 (0–0.35) umol/mmol). CT-abdomen demonstrated a suspicious L-adrenal mass measuring 4.5×4.3 cm. MIBG scan showed uptake in the region of L-adrenal consistent with a neuroendocrine tumour. Alpha-blockade was established and patient later underwent L-adrenalecetomy. Histopathology confirmed phaeochromocytoma. Metanephrines normalised post-operatively but SST demonstrated inadequate adrenal response. He is currently on glucocorticoid replacement and annual pituitary assessment. This case demonstrates synacthen-induced phaeochromocytoma crisis. There are several case reports of exogenous glucocorticoid-induced phaeochromocytoma crises but no reports of Synacthen- or ACTH-induced crisis were found. The likely mechanism is the effect of glucocorticoid surge secondary to synacthen stimulation leading to augmented effect on enzymes involved in catecholamine biosynthesis and release, e.g. phenylethanolamine N-methyltransferase (PNMT).

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EP1176

Ectopic ACTH-secreting pituitary adenomas located in the sphenoid sinus: an overview

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Background

Ectopic pituitary adenomas are defined by the presence of adenomatous pituitary tissue outside the sella and distinctly separate from the pituitary gland. Ectopic ACTH secreting pituitary adenomas (EAPAs) are a rare cause of Cushing’s syndrome. Detecting these radiologically can prove difficult, in part, due to their typically small size and unpredictable anatomical location.

Aim

We reviewed the current literature on all previously reported EAPAs within the sphenoid sinus.

Results

Twenty cases of EAPAs have been reported in the literature to date. In most cases, ectopic ACTH pituitary adenoma within the sphenoid sinus will manifest with symptoms of hormonal excess, have an obvious sphenoid sinus mass on pre-operative imaging and will demonstrate resolution of hypercortisolism after surgical excision if located and removed.

Conclusions

In ACTH-dependent Cushing’s syndrome, if, despite comprehensive testing, the source of excess ACTH remains occult (including negative work up for ectopic ACTH syndrome) thought should be given to the possibility of the patient harbouring an EAPA. Careful review of the neuroimaging to identify potential lesions, especially when pituitary imaging is not conclusive, is imperative. In the context of negative ‘MR’ imaging, the presence of EAPAs should be considered. Appropriate investigation and resection of such lesions may prevent unwarranted hypophysectomy, radiotherapy and/or adrenalectomy and result in long term and persistent remission.

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EP1177
Cushing’s disease and co-existing phaeochromocytoma
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Clinical presentation
We report a 46 year old female who presented with a 1 year history of bruising, thin skin and weight gain. In addition, she reported flushing of her chest, heat intolerance, palpitations and abdominal pain. On clinical examination she appeared cushingoid, blood pressure was elevated at 160/98 mmHg.

Investigations
Biochemical investigations indicated ACTH-dependent Cushing syndrome; 24 h UFC 300 μg (0–50); ACTH 119 pg/ml (8–42); midnight salivary cortisol 950 ng/dl (<100). MRI pituitary demonstrated a sellar lesion; 14×9×9 mm suggestive of a pituitary macroadenoma. To investigate the symptoms of flushing and palpitations, plasma fractionated catecholamines and metanephrines were performed and were elevated; norepinephrine 822 pg/ml (80–520), epinephrine <10 pg/ml (10–200), dopamine <20 pg/ml (0–20), normetanephrine 1250 pg/ml (18–101), metanephrine 34 pg/ml (12–67). CT abdomen revealed a lipid poor right adrenal mass measuring 17×36 mm with Hounsfield units of 47, consistent with a phaeochromocytoma.

Management
The patient started phenoxybenzamine and subsequently uptitrated the dose for three weeks prior to elective adrenalectomy. A robotic right trans-abdominal lateral adrenalectomy was performed without complications, histology confirmed phaeochromocytoma. One month post-adrenalectomy plasma fractionated catecholamines and metanephrines were normal. The patient continued to be hypercortisolemic post-op. 6 weeks after adrenal surgery transsphenoidal resection of the pituitary mass was performed, the histology revealed an adenoma which was diffusely positive for ACTH, it did not stain with any other anterior pituitary hormones. At 3 months post-pituitary surgery, she had normal plasma metanephrines and 24 h UFC levels with no visible residual disease on MRI.

Discussion
Phaeochromocytoma is associated with excess morbidity and mortality if undiagnosed, it was therefore fortuitous that this diagnosis was made prior to pituitary surgery. Clinicians should be alert to the rare association of undiagnosed, it was therefore fortuitous that this diagnosis was made prior to pituitary surgery. Clinicians should be alert to the rare association of phaeochromocytoma in patients with clinically significant pituitary adenomas, and pursue further work up if clinically indicated.

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EP1178
Cushing’s disease from an ectopic parasellar adenoma
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Background
Most cases of Cushing’s disease originate from the pituitary, rarely the source of excess ACTH is from an ectopic pituitary adenoma.

Case
A 34-year-old woman had a 12-month history of a labile mood, weight gain, easy bruising, irregular menses and hypertension, she appeared cushingoid. Biochemical investigations demonstrated hypercortisolism: 24 h urine-free cortisol 520.7 μg (4–50), ACTH 152 pg/ml (8–42); midnight salivary cortisol 510 ng/dl (<100). 0800 h serum cortisol 28.5 mcg/dl (6.5–26) after a 1 mg overnight dexamethasone suppression test (DST). There was a 70% suppression of cortisol after an overnight high dose (8 mg) DST, and a 50% increase in ACTH during a corticotropin releasing hormone (CRH) test. MRI of the sella revealed an atypical enhancing mass (0.7×0.9×0.5 cm) lying above the pituitary gland, the pituitary gland was normal. Transsphenoidal exploration without inferior petrosal sinus sampling (IPSS) was undertaken. A lesion located wholly in the suprasellar intracranial space, with its inferior aspect lying on but not transecting the diaphragm sella, was removed. No tumour was identified within the sella or pituitary. Pathology revealed a pituitary adenoma, with ACTH immunopositivity. At 6 months follow-up she remains in remission, with preservation of anterior pituitary function.

Discussion
Various locations of ectopic pituitary adenomas have been reported, including the sphenoid sinus, nasopharynx, intracerebral sinus. Ectopic pituitary tumours have been proposed to arise mainly from pituitary rest cells from the embryonic remnants of Rathke’s pouch, from aberrant migration of pituitary cells or from neoplastic transformation of the pharyngeal pituitary. They can be difficult to diagnose because of their small size and unusual locations.

Conclusion
In patients with Cushing’s disease, careful preoperative review of sellar imaging is imperative. These ectopic tumours are not always visible on imaging, and may explain why some patients with Cushing’s disease have residual hypercortisolism after hypophysectomy.

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EP1179
Two cases of observation of teenagers after prostatectomy volume transnasal pituitary education followed by recombinant growth hormone therapy Dzhintropinom (Eurofarm)
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Purpose
To examine two cases of teenagers after transnasal removal of pituitary volume of education followed by recombinant growth hormone therapy Dzhintropinom (Eurofarm).

Materials and methods
During the period of 2014 in the department of paediatric endocrinology and neuroendocrinology RSNPM Endocrinology Center MoH (Tashkent), we examined two male patients, including the patient F., 2.5 g of a craniofacial yngioma, and the second patient For 15 years with inactive pituitary adenoma. Patients underwent the following range of studies, including clinical, biochemical blood tests and urine tests, radioimmunoassays hormonal methods of blood tests (prolactin, IGF1, GH, TSH, ACTH, LH, FSH, free testosterone, cortisol, thyroxine), ECG, ultrasound genitals and others. All patients underwent MRI of the pituitary gland. Both patients in 2013 was carried out surgery – transnasal pituitary prostatectomy. In both postoperative patients developed panhypopituitarism: diabetes insipidus, GH deficiency (0.03 nmol/ml at a rate of greater than 2 nmol/l), IGF1 (<35 ng/ml), and hypogonadotrophic hypogonadism and short stature patient K. 15 I. In this regard, both patients were assigned to hormone replacement therapy, which included desmopressin, levothyroxine, and genetically engineered growth hormone Dzhintropin (Eurofarm). The latter was assigned based 0.033 g/kg per day, daily, subcutaneously, in the evening, in the forearm, within 6–8 months.

Results
Based on the investigations, it was found that both patients showed a positive trend during therapy Dzhintropinom, namely significantly increased basal and stimulated (with sample klofilinom) levels of growth hormone. Furthermore, there was a noticeable improvement in the dynamics of growth of the body, namely an average of 6 months to 6 cm.

Conclusions:
patients (children and adults).

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**EP1180**

The case of a combination of pituitary hypoplasia and achondroplasia have a child (boy 6 years old)

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Purpose

To describe the case of a combination of pituitary hypoplasia and achondroplasia have a child (boy).

Material and methods

Under our outpatient observation is a boy Abdalalatov S., born in 2008, lives in Samarkand. From history: The child was born in the closely related parents' marriage (sisters' children). Height at birth 50 cm, weight 3000 g, cried and took the breast immediately. Psycho-motor development – late. Constantly under the supervision of a paediatrician, getting a massage. Addressed to the endocrinologist for the first time in 2014. In RSPMC Endocrinology MoH patients underwent the following range of studies, including clinical, biochemical studies - complete blood count, radiomunoussay methods hormonal blood tests (prolactin, IGF1, GH, TSH, cortisol, thyroxine), ECG, ultrasound of internal organs, pituitary MRI, X-ray of hand and spine.

Results and discussion

According to parents, the patient complains of stunting, trouble walking. On examination it was found: objective: Growth 103, 5 cm, weight – 29 kg. Growth Deficit – 20 cm, underweight – 9 kg. Pubertal status: ADH0, testis 3.0 × 3.0 ml, penis length of 1.0 cm. On the side of hormonal studies: STG – 1.4 mIU/l (normal in children aged 5–16 years 2.1 ± 0.53 mIU/l), St. T4 – 124 nmol/L (60–160), TSH – 1.9 mIU/l (normal 0.17 ± 4.05), IGF1 – 101 nmol/l, MRI sella (from 01.12.2014 g) was discovered pituitary hypoplasia: height 0.1 cm anteroposterior size – <0.4, width – up to 0.4 cm. On radiographs of the spine (from 02.12.2014) was: bone age from 3 to 24 months, the appearance of a violation of the sequence of points of ossification. Growth areas are open, narrowed, shortening of the phalanges. Cystic fibrosis? Gipohondroplazia? On radiographs of the spine (from 02.12.2014 city). S-shaped scoliosis of the spine. Dysplasia of both hips, thighs complicated dislocation on both sides. Thus, on the basis of the foregoing, the clinical diagnosis was exhibited: est. Achondroplasia. Sop. Pituitary hypoplasia. OSL. Growth retardation and skeletal development. S-shaped scoliosis of the spine. Dysplasia of both hips, thighs complicated dislocation on both sides. Patient was recommended to hormone replacement therapy: levothyroxine 50, genetically engineered growth hormone, and thyroid medications, calcium, vit D3. The patient was recommended consultation and treatment and also a podiatrist.

Conclusions

Patients with achondroplasia recommended MRI of the pituitary to identify possible hypo – or aplasia pituitary; 2) In the presence of hypopituitarism in patients with achondroplasia need appropriate hormone replacement therapy.

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**EP1182**

17 ß hydroxylase enzyme deficiency with hyperaldosteronism

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Background

Congenital adrenal hyperplasia (CAH) resulting from 17 ß hydroxylase enzyme deficiency (17OHD) is a rare autosomal recessive disorder. More than 150 cases were reported in the literature. Patients with 17OHD were reported to have hypoadosteronism.

Case

A 16-year-old female referred to endocrinology outpatient clinic from family medicine department with the absence of a secondary sexual characteristics and primary amenorrhea. On physical examination she had no pubic or axillary hair. She has Tanner stage I breast development and female external genitalia. Her height was 158 cm, weight 51 kg and blood pressure was 155/90 mm/Hg. Her karyotype was 46XX and bone age was nine years. Initial laboratory tests showed that serum glucose, urea, creatinin, sodium levels were normal: potassium level was low. Serum levels of 17 ß hydroxyprogesterone (17-OHP), dehydroepiandrosterone sulphate (DHEA-S), androstenedione, cortisol, plasma renin activity (PRA), oestriol (E2) were low and serum aldosterone, adrenocorticotropic hormone (ACTH), deoxycorticosterone (DOC), luteinizin hormone (LH), follicle stimulating hormone (FSH) was high (Table 1). All aldosterone and PRA values were obtained in upright position. Abdominal MRI showed rudimentary uterus and a nodular development in the left adnexal area suggestive for ovary. The adrenal gland did not show significant adrenal hyperplasia and there was no mass lesion. Her blood pressure (110/80 mm/Hg) and potassium (3.9 meq/l) became normal after beginning hydrocortisone tablet 10 mg in the morning, 10 mg at noon and 5 mg in the evening. Subsequently the patient was started on cyclic oestrogen for maturation of secondary sex characteristics. At the following visit we show that development was started but her blood pressure was 180/100 mm/Hg. Her potassium level was 3.4 meq/l we raised the total hydrocortisone dose to total 30 mg per day and added 25 mg spirinolactone. Few days later her self monitoring blood pressure results were between 160/100–140/90 mm/Hg. Amlopidin 10 mg was started. Few days later blood pressure became normal. At the last visit her blood pressure was 120/80 mm/Hg serum potassium (3.9 meq/l), aldosterone (194 pg/ml), PRA (0.762 ng/ml).

Table 1 Baseline biochemical and hormonal test results

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium (meq/l)</td>
<td>2.9</td>
<td>3.5–5.2</td>
</tr>
<tr>
<td>PRA upright (ng/ml/sa)</td>
<td>&lt;0.2</td>
<td>0.2–6</td>
</tr>
<tr>
<td>Aldosterone upright (pg/ml)</td>
<td>385.45</td>
<td>20–220</td>
</tr>
<tr>
<td>ACTH 0800 h (pg/ml)</td>
<td>106</td>
<td>10–46</td>
</tr>
<tr>
<td>Cortisol 0800 h (ug/ml)</td>
<td>1.75</td>
<td>6.2–19.4</td>
</tr>
<tr>
<td>DHEA-S (ug/ml)</td>
<td>6.33</td>
<td>25–250</td>
</tr>
<tr>
<td>DOC (ng/dl)</td>
<td>250</td>
<td>4–12</td>
</tr>
<tr>
<td>17-OHP (ng/dl)</td>
<td>4.63</td>
<td>31–217</td>
</tr>
<tr>
<td>Total testosterone (ng/dl)</td>
<td>6.33</td>
<td>10–70</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>34</td>
<td>follicular:2.12–10.89</td>
</tr>
<tr>
<td>FSH (mIU/ml)</td>
<td>89</td>
<td>follicular:3.85–8.78</td>
</tr>
<tr>
<td>E2 (pg/ml)</td>
<td>&lt;20</td>
<td>follicular:27–122 luteal:1.20–12.86</td>
</tr>
<tr>
<td></td>
<td></td>
<td>luteal:1.79–5.12</td>
</tr>
</tbody>
</table>

Discussion

Patients with 17OHD have been reported to have hypoadosteronism. We report a different variant of 17OHD with increased aldosteron and decreased renin production. We reviewed the literature and found at least 17 cases of 17OHD with normal aldosterone and 18 cases with elevated aldosterone levels.
The explanation for that is salt retaining due to volume expansion effects of the high concentrations of DOC, with consequent transcriptional down regulation of aldosterone synthase. The mechanism of normal and high aldosterone levels remains unclear. One explanation for this different aldosterone levels can be the cross reaction of the antisera for aldosterone measurement. Beckman Coulter radioimmunoassay kit was used for aldosterone measurement in this case. The antibody used in this kit is highly specific for aldosterone. According to the direction of use of this kit, low reactivities were obtained with several molecules (corticosterone, 18-OH corticosterone, etc.). Patients who have been regularly exposed to animals or received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies that interfere with immunoassays; but there was no suspicion of having these antibodies in our patient. At the last visit her self-monitoring blood pressure results, serum potassium, aldosterone and PRA levels were all in normal limits as a result of hydrocortisone, spironolactone, amiodipin treatment. We terminated cycling oestrogen use for four weeks before these tests because oestrogen, progesterone replacement may also interact with steroidogenesis. We thought that the radioimmunoassay in this study is reliable. Although the cross reaction possibility remains. Cases of 17OHD with hyperaldosteronism could be a variant of 17 OHD and could be genetically determined.

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EP1183
Laryngeal carcinoma in acromegalic patients: a rare case
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Introduction
Acromegaly is a very rare disease with persistent GH secretion due to excessive release of liver IGF1. The risk of malignancy, particularly colon cancer, is increased in acromegalic patients. But no evidence is found in the literature associated increasing of laryngeal carcinoma in acromegalic patients. We aimed to present this case that laryngeal carcinoma should be considered in acromegaly by the clinicians.

Case report
A 51-year-old male patient was diagnosed as acromegaly due to pituitary macroadenoma with the expansion of the suprasellar area localisation in flood. He was operated the right pterional craniotomy at December 2003. Postoperatively he was given the 28×200 GY doses of radiotherapy linear treatment because of residual mass lesion in screening control MRI. He was medicated somatostatin analogues without cured by radiotherapy. In 2011, he admitted to our clinic with hoarseness and left ventricle mass extending was found by direct laryngoscopy. Polypoid soft tissue mass with narrowing the air column of the left vocal cord was detected by simultaneously neck CT. Biopsy revealed squamous cell carcinoma. Total laryngectomy with left lateral neck dissection was performed. Malignancy was not detected in PET CT which made of re-staging. Colonoscopy and endoscopy was performed and two polyps were found. As a result of pathology remains unclear. One explanation for this different aldosterone levels can be the cross reaction of the antisera for aldosterone measurement. Beckman Coulter radioimmunoassay kit was used for aldosterone measurement in this case. The antibody used in this kit is highly specific for aldosterone. According to the direction of use of this kit, low reactivities were obtained with several molecules (corticosterone, 18-OH corticosterone, etc.). Patients who have been regularly exposed to animals or received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies that interfere with immunoassays; but there was no suspicion of having these antibodies in our patient. At the last visit her self-monitoring blood pressure results, serum potassium, aldosterone and PRA levels were all in normal limits as a result of hydrocortisone, spironolactone, amiodipin treatment. We terminated cycling oestrogen use for four weeks before these tests because oestrogen, progesterone replacement may also interact with steroidogenesis. We thought that the radioimmunoassay in this study is reliable. Although the cross reaction possibility remains. Cases of 17OHD with hyperaldosteronism could be a variant of 17 OHD and could be genetically determined.

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EP1184
Psychotropic medication – endocrine consequences

Given the increasing incidence in psychiatric pathology, adverse reactions of psychotropic medications, especially the metabolic and endocrine side effects, are encountered more frequently in clinical practice. We present the cases of two female patients with psychiatric pathology, in whom the specific treatment was accompanied by significant endocrine adverse reactions, making the tumoural differential diagnosis very difficult. The first case is of a patient aged 61 years, known with schizophrenia from the age of 27 years and treated for many years with valproic acid, who preented to our clinic for severe virilising syndrome with a total serum testosterone of 9.2 ng/ml, rising the suspicion of ovarian or adrenal carcinoma. The second case is of a female patient aged 24 years, diagnosed with depressive disorder, in whom treatment with escitalopram and valproate was accompanied by amenorrhea-galactorrhoea syndrome and severe hyperprolactinaemia of 224 ng/ml (more specific for a macroadenoma). The pituitary CT scan revealed a microadenoma of 0.40×0.4 cm, generating important issues regarding differential diagnosis. Although endocrine side effects are often not life threatening and are less frequent than neurological side effects, such as sedation, extrapyramidal syndrome and anticholinergic disorders, recognizing and correcting them is the key to successful therapy and ensures compliance of the patient with psychiatric pathology.

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EP1185
Acrornegaly due to McCune-Albright syndrome
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1Endocrinology Research Centre, Moscow, Russia; 2Burdenko Neurosurgical Research Institute, Moscow, Russia.

A 27-year-old male patient during past 10 years noted a gradual change in his appearance, but began to seek a medical attention only 1.5 years ago due to reduced vision. Hormonal tests from March 2013 revealed marked elevation of GH to 106 mU/l (ref. values <20), and IGF1 to 567 ng/ml (121–336), decrease in testosterone levels to 1.91 ng/ml (3–12), with cortisol, LH, FSH, PRL, TSH values within the reference range; MRI of the brain showed a 4×7 mm adenoma of the anterior part of the pituitary, CT brain scan with contrast described polisodic dysplasia of the skull bones. From September 2013 octreotide depot injections therapy was initiated 10 mg per 28 days, with further increase to 20 mg per 28 days. In January 2014 levels of GH and IGF1 were still high in spite of medical treatment – 119 mU/l and 1033 ng/ml respectively. In Apr 2014, at admission to Endocrinology Research Centre at the age of 27 years the patient was 205 cm tall and weighed 124 kg (BMI 29.5 kg/m²). ‘Café au lait’ pigmentation of the skin was noted at the chest, back, and abdomen. His facial features were acromegoid with sloped towered skull. Lab tests confirmed the presence of the active acromegaly (GH – 117 mU/l, IGF1 – 1412 ng/ml), brain MRI with contrast showed a marked increase in the size of previously described adenoma (17×23×14 mm), and progression of the fibrous dysplasia (predominantly hypointense on T1) of the skull base, parietal, temporal bones, scales of the frontal and occipital bones, hypopneuma-tization of frontal sinus and ethmoidal labyrinth, narrowing of the internal and the external auditory canals on the left. All these symptoms allowed us to suspect a McCune-Albright (MAS) syndrome. The progressive clinical course of the disease, insensitivity to octreotide treatment was the basis for the choice of further surgical treatment despite the pronounced fibrous dysplasia of the skull base. In Oct 2014 at Burdenko Neurosurgical Research Institute the patient underwent endoscopic endonasal removal of tumor using navigation BrainLab. Postoperatively levels of GH and IGF1 decreased to –27 mU/l and 856 ng/ml, visual function had markedly improved. He was then followed on depot octreotide injections 30 mg per 28 days and caborergine 2 mg per week with later dose adjustments.

Conclusions
The treatment of acromegaly in the setting of MAS is characterized by multiple challenges that require the participation of a team of experienced endocrinologists and neurosurgeons.

Disclosure
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EP1186
Spontaneous pneumocephalus associated with a giant craniohypophysial neoplasia
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Introduction
Pneumocephalus is defined as the presence of air within the cranial cavity. It is usually associated with neurosurgical procedures but can also be caused by craniofacial trauma, infections and tumours of the skull base and rarely can occur spontaneously. Neoplasms involving the pituitary fossa are unusual causes of spontaneous pneumocephalus.

Case report
A 39-year-old man presented in the emergency department with significant visual loss, headache and rhinorrhoea. He had no previous history of head trauma or medical illnesses. He complained for increasing fatigue, headache and progressive loss of libido for the last 20 years. On physical examination his height was normal but he had low blood pressure and orthostasis. Optical field examination revealed preservation of central vision only. Initial laboratory examinations showed anaemia. All measured pituitary hormones were low except prolactin. The patient was diagnosed with panhypopituitarism. In the emergency department the patient brought with him a skull radiograph lateral view which showed air in the intracranial cavity. He underwent a brain MRI. A midline large space-occupying inhomogeneous mass was seen, extending and filling the suprasellar cistern, pituitary fossa and sphenoid sinus. It was characterised by cystic lesions separated by thin diaphragms and filling by fluid of increased signal intensity on T2 due to increased protein concentration. Haemorrhagic elements were demonstrated inside the solid contents at the left part of the mass. The aforementioned characteristics were indicative of a giant craniohypophysial neoplasia. The patient underwent neurosurgical debulking of the tumour and evacuation of the air collection. He was placed in replacement therapy with marked improvement.

Histological examination confirmed the diagnosis of craniohypophysial neoplasia.

Conclusion
Although extremely rare, spontaneous pneumocephalus should be considered as a possible diagnosis in patients with large pituitary lesions, rhinorrhoea and non-specific neurological manifestations. Early treatment of this potentially life-threatening disorder improves surveillance of these patients.

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EP1187
Late diagnosis, early response - or the story of a smile
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We present the case of a 33-year-old male who addresses an endocrinology service for the first time in May 2014 for marked asthenia, drowsiness, muscular aches, and a delay in growing. The physiological exam showed difficulties in communicating and relation with the others based on his own negative image of himself, lack of self-trust, auto-isolation tendency, state of depression. We raised the suspicion of a panhypopituitarism confirmed by the lab exams that describe a somatotrope, tireotrope, corticotrope and gonadotrope deficit. The patient doesn’t associate diabetes insipidus. In this conditions the patient associates a delay of bone age that is of approximately 14 years with a height at –1 s.d. for adult age (height velocity the last 2 years as declared was approximately 15 cm per year) and also a poor bone mass density Z-score = -1.8. The IRM showed an empty sella. We initiated treatment with prednisolone on which the blood pressure raised till 110/70 mm/Hg, thyroid hormones and testosterone to complete his bone growth after which we will be placing him on growth hormone substitution for adults. After 6 months of treatment his general estate improved: his blood pressure till 110/70 mm/Hg, thyroid hormones and testosterone to complete his bone growth. On the appearance of a smile.

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EP1188
Ipilimumab-induced hypophysitis in cancer patients
Christian Lafuente1, Karina Arcano1, Fernando Guerrero2, A Marengo3, I Peró4, Amara Soria1, Juan José Diez5, Carlos Villalbana6 & Pedro Iglesias7

Introduction
IPI is a human monoclonal antibody against cytotoxic T lymphocyte antigen-4 (CTLA-4), which enhances stimulation of cytotoxic T lymphocytes, resulting in an immune response against the tumour. This drug-induced hyperactivity of the immune system can lead to serious adverse effects including endocrine disorders such as autoimmune hypophysitis, thyroiditis and adrenal insufficiency.

Objective
To report our experience on ipilimumab-induced hypophysitis (IIH) in patients with advanced cancer.

Results
Four patients (three men (75%); aged 67.5 ± 8.7 years (range, 59–75)) with advanced cancer (three melanomas and one prostate cancer) were recruited. The clinical presentation of IIH was similar in all cases regardless of the underlying tumor. IIH developed after 12–19 weeks of starting treatment, usually between two and four ipilimumab cycles. Main symptoms were fatigue (n = 3) and headache (n = 2), nausea (n = 2) and vomiting (n = 2). IIH was associated with partial or total hypophysitis in three cases. Pituitary hormone deficiencies most frequently affected were corticotrophin (ACTH, n = 3), thyrotrophin (TSH, n = 3) and gonadotrophins (FSH and LH, n = 3). Two patients showed prolactin and growth hormone deficiencies. One patient did not develop any pituitary hormone deficiency although magnetic resonance imaging (MRI) of the pituitary showed morphologic changes of hypophysitis. MRI study showed enlarged pituitary in three patients. All patients were treated with high steroid doses (>0.5 mg/kg per day of prednisone or equivalent). After 28 months (range, 22.2–35.4) of follow-up, three patients remained with steroid hormone replacement therapy and two patients with replacement doses of levodopa. One patient recovered thyroid function. IIH is an immune-related adverse event that can compromise the patient’s life because of the possibility of development of adrenal and thyroid insufficiency in a high percentage of patients. Glucocorticoids are the treatment of choice. Hormone replacement therapy is indicated according to hormone deficiencies. Patients receiving immunomodulatory therapies should be closely monitored by baseline and follow-up hormone assessment.

DOl: 10.1530/endoabs.37.EP1188

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EP1189
A case report of two sibling with untreated congenital adrenal hyperplasia
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1Gaziantep Doktor Ersin Arslan Hospital, Gaziantep, Turkey; 2Medical Faculty, Gaziantep University, Gaziantep, Turkey.

Introduction
The term congenital adrenal hyperplasia (CAH) encompasses a group of autosomal recessive disorders, each of which involves a deficiency of an enzyme
involved in the synthesis of cortisol, aldosterone, or both. Deficiency of 21-hydroxylase, resulting from mutations or deletions of CYP21A, is the most common form of CAH, accounting for more than 90% of cases.

Case report
Two female siblings were referred to endocrine clinic with the complaint of amenorrhea and hirsutism. In their medical history, The elder sister presented to the paediatrics team at 4 years old with progressive enlargement of the clitoris, acne, muscular built and labioscrotal hyperpigmentation. There was no history of salt-losing crisis or hypoglycaemia. A diagnosis of CAH was made. The younger sister at 2 years old, presented with clitoral enlargement and acne. Similar investigations were performed and the diagnosis of CAH was confirmed. Both sisters were started on hydrocortisone upon diagnosis. Clitoral reduction and vaginal reconstruction surgery was performed for both sisters soon after the diagnosis. Although the seriousness of the illness was explained to their parents, replacement therapy were interrupted by them due to difficult social and economic status of the family, who lived for many years without basic medical care. 15 years later, at the age of 19 and 17; they were seen at the endocrine clinic. On physical examination, they were noted to have a short stature with body height of 1.48 and 1.52 cm. Physical examination revealed extreme virilisation. They were observed marked hirsutism, male type pubic hair, deepening of the voice, clitoromegaly, without breast development and primary amenorrhea. Hormonal analysis showed significantly elevated serum levels of 17-OHP (416, 513 nmol/l) and serum testosterone (30, 49 nmol/l). Mutational analysis of the CYP21A2 gene by multiplex ligation-dependent probe amplification and by polymerase chain reaction (PCR) followed by direct DNA sequencing showed homozygotes I172N mutation.

Discussion
Here we present two sisters with classic simple virilising form of 21-OHD with mutation. By multiplex ligation-dependent probe amplification and by polymerase chain reaction (PCR) followed by direct DNA sequencing showed homozygotes I172N mutation.

Introduction
Phaeochromocytoma and Cushing syndrome are two uncommon endocrine conditions. The association of these two conditions is very rare and not well elucidated. We report an association of a phaeochromocytoma with an ACTH-dependent Cushing syndrome.

Case report
A 32-years-old female patient was admitted in the endocrine department for paroxysmal hypertension diagnosed in the immediate post partum period. She reported sweating and palpitation crises occurring with hypertensive peaks. Her blood pressure on treatment (calcic inhibitor and central antihypertensive) was 95/70. Clinical examination didn’t reveal any evidence for Cushing syndrome. Laboratory findings showed hypokalaemia at 3.8 meq/l with a hyperkaliuresis. CT-scan revealed a 34×34 mm homogenious right adrenal mass. Urinary metanephrines were very high confirming phaeochromocytoma. Cortisol after low dose dexamethasone suppressing test (LDDST) was 60 nmol/l confirming the diagnosis of Cushing syndrome. ACTH was 39 ng/l and cortisol was suppressed by high dose dexamethasone test. Pituitary MRI was normal. The patient had an endoscopic adrenalectomy. Histology concluded to phaeochromocytoma. After surgery, hypertension and hypokalaemia disappeared. Urinary metanephrines became normal and cortisol was suppressed by LDDST.

Conclusion
This is a rare case of phaeochromocytoma with a paraneplastic ACTH secretion causing a subclinical Cushing syndrome.

EP1192
Coexistence of ovary tumour, congenital adrenal hyperplasia and triple translocation involving chromosome 9,11 and 12: Initial steps of defining new syndrome?
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Introduction and aim
Congenital adrenal hyperplasia (CAH) is rare autosomal recessive disease. CAH due to 21-hydroxylase deficiency accounts for 95% of cases. We aim to define in this report 59-year-old woman with simple virilizing type CAH who diagnosed granulosa cell tumour and 1172N mutation in the CYP21A as well as triple translocation involving chromosome 9p, 11p and 12p at first time in the literature.

Case report
A 59-year-old woman was applied to our clinic complained with abdominal pain and distension. She had irregular menstrual cycle per 3–4 month and hypomenorrhoea. She had gone through the menopause at 40 years old. She had never become pregnant. In physical examination her breast tissue had not developed and virilism was determined (modified Ferriman galvsey score >16). A palpable solid mass was detected in the right of abdomen. Ambigious genitalia, clitoromegaly and hyperpigmentation were found. In computerized tomography giant ovariann mass in mesentery tissue was viewed. The mass (3500 g) was removed with the right tubo-ovarian structures. The granulosa cell tumour was diagnosed by the immunohistochemical examination. The high serum concentration of 17-OH progesteron measured at baseline and after 250-μg bolus of synthetic ACTH. In genetic analysis, we screened for six point mutations, large deletions, and noncommon mutations using restriction fragment length polymorphism (RFLP) methods, PCR, and sequencing of CYP21 gene respectively. The patient was detected to be homozygote for the I172N mutation. In addition, 50% of the metaphases examined had triple translocation (t9; 11; 12) between chromosomes 9p, 11p and 12p.

Conclusion
The I172N mutation in the CYP21A accompanied with t9;11;12 translocation did not define previously in patients with CAH. This mutation may be sign of a new syndrome or a co-incident that triggered to granulose cell tumour.

EP1193
Case report: an acromegalic patient presented with dysphagia
Feyzi Gokosmanoglu, Cigdem Tura Bahadir, Elif Klici Kan & Aysegul Atmaca
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Introduction
Acromegaly is a chronic disease characterized by prognatism, frontal bossing, coarsened facial features, enlarged hands and feet due to overproduction of growth hormone (GH) generally by a pituitary adenoma. Here, we aimed to present an acromegalic patient presented with retropharyngeal hypertrophy first time in the literature.

Case report
65-year-old female patient had been referred to our department from otorhinolaryngology outpatient-clinic, where she had admitted with sensation of something stuck in throat for 2 years, upon finding overgrowth in avula and oropharyngeal structures. She had symptoms of sweating, overgrowth in hands, feet, nose and lips. She had type 2 diabetes mellitus and hypertension history.

Physical examination revealed coarssened facial features, deepened nasolabial folds, prognatism, tongue and oropharynx hypertrophy. Her blood glucose level was 173 mg/dl, IGF1 level was 929 ng/dl (normal range: 94–166 ng/dl) and GH level was 4.2 ng/dl. The lowest GH level during growth hormone suppression test was 3.8 ng/dl. Levels of other pituitary hormones were normal. Head and neck...
magnetic resonance imaging (MRI) revealed expansion of orofacial bones and hypertrrophy of the retropharyngeal soft tissue. MRI of pituitary gland revealed a 8 × 6 mm microadenoma with well defined boundaries in the pituitary gland. The patient was diagnosed with acromegaly and consulted with neurosurgery department regarding surgery.

Discussion
Acromegaly is a condition that should be considered in cases of soft tissue hypertrrophy in oral cavity, teeth occlusions, diastema and teeth prosthesis discrepancies.

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EP1194
A rare case of adrenal histoplasmosis presenting as adrenal insufficiency and hypogonadism following a visit to bat caves
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Background
Histoplasmosis is an opportunistic fungal infection that commonly affects immunocompromised individuals. Histoplasmosis may be asymptomatic or may present with progressive systemic manifestations (pulmonary or disseminated). We report a case of a 76 year old immune competent man presented with 8 weeks history of general malaise and lethargy, intermittent night sweats, a productive cough, weight loss of 2.5 stones in two months and low grade fever. He had completed two courses of antibiotics with no resolution of his symptoms. He reported no history of tuberculosis contacts. Significant history was of travel to Malaysia and a visit to bat caves 2 years prior to the onset of symptoms. On admission, he was haemodynamically stable and his initial blood tests were normal apart from raised CRP of 80 mg/l. Chest XRay was normal. CT of sinus showed minimal mucosal thickening. CT chest, abdomen and pelvis revealed large bilateral adrenal heterogeneous masses measuring 6.1 × 4.5 × 3.7 cm on the right, and 6.4 × 6.2 × 4.3 cm on the left. Adrenal biopsy showed fungal spores on microscopy. He was started on antifungal therapy for likely adrenal histoplasmosis and discharged home. He was readmitted 2 months later with a GCS of 6/15, Temperature 38°C, and hypotensive episodes. He had normal CT and MRI brain results, negative blood cultures and unremarkable CSF studies. Echocardiogram excluded the vegetations. He was treated with intravenous empirical antibiotics and hydrocortisone. He was continued on his antifungal therapy. Initial short synacthen test showed normal response, however he became more tired and hyperpigmented with a subsequent short synacthen test showing a suboptimal response T0 = 333 nmol/l, T30 = 378 nmol/l. He also developed primary hypogonadism subsequently, thought to be due to effect of antifungals or due to histoplasmosis itself.

Conclusion
Adrenal histoplasmosis is rare, especially in immunocompetent individuals and should be considered as a differential diagnosis in any patient presenting with bilateral adrenal masses, constitutional symptoms and suggestive history. Also one should be vigilant about possible side effects of antifungals e.g. hypogonadism in this case.

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EP1195
Differential diagnosis of low renin hypertension – pseudohyypoaldosteronism type 2
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1Riga East University Hospital, Riga, Latvia; 2Riga Stradsins University, Riga, Latvia.

Introduction
Pseudohyypoaldosteronism type 2 (PHA2), also known as Gordon syndrome, is a rare inherited form of low-renin hypertension associated with hyperkalaemia and hyperchloraemia. PHA2 is the result of mutations in a family of serine-threonine kinases called with-no-lysine kinases (WNK) 1 and WNK4. These enzymes regulate electron channels in the aldosterone sensitive distal nephron, resulting in disrupted electron balance. PHA2 is a genetically and phenotypically heterogeneous entity, associated with high sensitivity to thiazides.

Case report
A 57 year old patient with anamnesis of treatment-naı¨ve hypertension and foramen ovale apertura enclosed with occluder was admitted to the hospital for surgery due to adrenal mass – a typical adenoma found on abdominal CT 5 years ago with the diameter of 1.7 cm. Laboratory test results excluded Cushing syndrome, but primary hyperaldosteronism was not suspected due to persisting hyperkalaemia. Abdominal MRI scan was repeated to evaluate the growth dynamics of the adrenal mass, revealing an enlarged left adrenal gland with a hypodense (9 HU) vascular mass 4.1 cm in diameter. Pre-operative testing revealed several laboratory abnormalities: hyperkalaemia 5.6 mmol/l (3.5–5.1) and hyperchloraemia 106 mmol/l (95–105), low plasma renin <0.5 μIU/ml (4.4–46.1), normal aldosterone 95.8 pg/ml (25.2–392.0), normal GFR 100.5 ml/min, acidic urine pH 4.8 and decreased potassium excretion 23 mmol per day (25–125). Considering the findings of low renin hypertension with hyperkalaemia and normal GFR the diagnosis of PHA2 was established. The patient was started on antihypertensive treatment with thiazide diuretic and underwent left adrenalect-omy. Histology confirmed to hormonally inactive adrenocortical adenoma, Weiss score 2.

Conclusions
The current case demonstrates the challenges of differential diagnosis of low renin hypertension depicting the characteristic findings of PHA2. It should be noted that upon correct diagnosis this form of low renin hypertension is easily treatable with thiazide diuretics.

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EP1196
The hidden liquorice: apparent mineralocorticoid excess caused by inadvertent exposure to liquorice root extract
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Introduction
Excessive consumption of liquorice can cause endocrine symptoms of apparent mineralocorticoid excess (AME). This is usually caused by excessive consumption of liquorice-containing sweets and native liquorice root but the different chemical compounds in liquorice may also be used in many other products where it is considered an additive and therefore not explicitly declared. Case
We here report a 21-year-old patient who exhibited severe symptoms of AME (oedema, spells of dizziness, headaches and peripheral paraesthesia as well as general and muscular fatigue) due to inadvertent excessive intake of liquorice. Blood samples showed low serum potassium (2.3–3.1 mmol/l, ref (3.5–4.6)) requiring potassium supplementation (40 mmol×2 daily) and high normal sodium (142–147 mmol/l, ref (137–145)). Measurement of 24 h urinary steroid metabolite excretion raised the suspicion of AME. Additional blood tests showed undetectable serum concentrations of aldosterone (<38 pmol/l, ref (50–360)) and renin (<2 × 10⁻⁷ IU/l, ref (6–60)). Pituitary function (thyroid hormones, prolactin, IGF1, IGFBP3) was normal. No obvious endocrine cause of AME could be established and the patient re-evaluated all personal dietary products. Liquorice root was present in several herbal teas and sugar-free chewing gums that had been consumed daily in large amounts. Cessation of usage of these products resulted in complete recovery of AME-related symptoms.

Conclusions
Our case report revealed other potential sources of liquorice than sweets including industrial sweeteners and flavouring agents that could potentially cause clinical symptoms. Clinicians should thus extend their medical history to a broader range of consumer products when suspecting AME.

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EP1197
From erectile dysfunction to brain subependymoma: a case report
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Case report
A 45 year old male patient was referred to our department regarding surgery.

Discussion
Acromegaly is a condition that should be considered in cases of soft tissue hypertrrophy in oral cavity, teeth occlusions, diastema and teeth prosthesis discrepancies.

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Intervention
Endocrinopathies are rare causes of erectile dysfunction and previously cases of hyperprolactinaemia and pituitary adenomas have been reported. Case report
We present the clinical case of a 27-year-old male, married for 4 years with no children, presented with possible infertility and erectile dysfunction which was previously interpreted as caused by a poor social and psychological situation in the family. After additional endocrinological (mildly elevated prolactin levels and reduced levels of testosterone) and radiological (skull X-ray, CT scan and MRI) an underlying subependymoma was discovered. The subependymoma was expanding in the sellar and suprasellar regions and pressing against the pituitary gland. The patient experienced occasional periorbital and temporal headaches, loss of appetite, general weakness. A Goldmann perimeter test was consistent with bitemporal hemianopia. The resulting endocrine disorder caused the problems which were subjectively at first mainly manifested as erectile dysfunction. The patient underwent a left-sided supraorbital craniotomy and complete surgical removal of the tumor at the Department of Neurosurgery. The histopathology findings described a subependymoma (G II). One year after surgery, the patient was in good general condition, but with bitemporal hemianopia, with atrophy of the right optic nerve and complete loss of vision in his right eye, panhypopituitarism and impotence. Two years later, with hormone replacement therapy (desmopressin, hydrocortisone, levothyroxine, testosterone undecanoate) there was no sexual dysfunction.
Conclusions
The case is an educative example about the necessity to keep possible intracranial lesions in mind when starting the workup of a patient presenting with erectile dysfunction. It may be of broad clinical interest not only for endocrinologists, but for practitioners in various fields.
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EP1198
Intestinal obstruction and bowel perforation as a presenting feature of a phaeochromocytoma
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Introduction
Phaeochromocytomas are a rare catecholamine secreting tumours that can present in multiple ways. The classic triad of symptoms consists of episodic headache, sweating, and tachycardia. Most patients do not have the three classic symptoms. Sustained or paroxysmal hypertension is the most common sign. Among less common symptoms and signs constipation has been described and few cases of megacolon and phaeochromocytoma have been published.
Case report
A 39 year-old man, with previous medical history of schizophrenia, autism and pulmonary tuberculosis with a partial left lobectomy, complained of abdominal pain of 3 days. An abdominal X-ray demonstrated dilated loops of small and large bowel with air-fluid levels in the upright position, abundant faecal remanis in the large bowel and faeculoma. Large bowel obstruction was suspected presenting an unfavorable evolution despite medical treatment. CT scan showed small and large bowel obstruction secondary to an intestinal malrotation with signs of sigmoid colon and rectum suffering and a left adrenal incidentaloma of 6 cm. An urgent surgical intervention was performed showing small bowel obstruction secondary to internal hernia secondary to dolichomegagasia and large bowel perforation with loculated abscess, performing sigmoidectomy, terminal colostomy and abscess exeresis. The postoperative evolution was good. The functionality of the adrenal incidentaloma was studied showing urinary metanephrines consistent with phaeochromocytoma. Treatment with phenoxybenzamine was started and left adrenalectomy was performed confirming the diagnosis of phaeochromocytoma. 1 year after the surgery he has not presented new episodes of bowel obstruction.
Conclusions
Intestinal obstruction is an important clinical condition that can present in association of phaeochromocytoma. Due to the risk of intervention in a patient previously not treated with alpha-blockade, if an adrenal incidentaloma is observed in a patient with intestinal obstruction, intestinal resection should be ruled out in order to prevent. surgery complications.
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EP1200
New onset Graves’ disease as a cause of an adrenal crisis in an unrecognised empty sella
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Introduction
A 66-year-old woman was admitted as an emergency with vomiting, hypotension and serum cortisol of 0.92 microg/dl indicative of adrenal failure. She was found to be hyperthyroid (TSH = 72 pmol/l).
Case report
She had hypotension (blood pressure 80/40 mm/Hg) She was fit and well till the age of 65. Endocrine assessment revealed deficiency in ACTH-cortisol, growth hormone, and gonadotropin, as well as low-normal T₄. On the day of his emergency admission he looked ill and dehydrated, though was fully conscious and cooperative. Heart rate was 110 beats/min (sinus rhythm), blood pressure 85/60 mmHg. There were no obvious features of infection, but there was marked tremor and thyroid bruit. She received treatment with intravenous fluids and hydrocortisone. Administration of large dose of methimazole (40 mg per day)

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resulted in gradual decrease in FT4. Pituitary MRI showed empty sella. The patient was found to have increased titre of antithyroperoxidase (anti-TPO) and antithyroglobulin (anti-TSHR) antibodies (2100 IU/l (ref. range <40) and 3.7 IU/l (ref. range <1.0), respectively). She was referred for radioactive iodine treatment. Iodine uptake scan performed prior to radioidine administration confirmed uniformly increased iodine uptake consistent with Graves’ disease.

Discussion

We encountered a patient with unrecognised adrenocortical disease due to empty sella, in whom development of Graves’ hyperthyroidism caused an adrenal crisis. The presence of hypopituitarism does not preclude the development of autoimmune thyrotoxicosis.

Conclusion

Our case illustrates coexistence of hypopituitarism and clinically significant autoimmune thyroid disease. The presence of hypopituitarism does not preclude the development of autoimmune thyrotoxicosis.

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EP1201

Klinefelter syndrome with portal vein aneurysm: case report

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Introduction

Klinefelter syndrome (KS) is the most common chromosomal disorder characterized by clinical features of hypogonadism and infertility. Portal vein aneurysms are very rare clinical findings. Reported cases are increasing due to use of modern imaging techniques in clinical practice.

Case report

19-year-old man was admitted to our hospital with complaints of abdominal pain, nausea, and vomiting associated with eating. He was recently diagnosed with KS by chromosomal analysis, which was performed because of eunucoid appearance and gynecomastia. On physical examination, lungs were clear and heart beats were regular. No abdominal tenderness was found and no enlarged liver or spleen was palpated. Laboratory studies revealed: white blood cell counts, 6.600 mm3; haemoglobin, 14.6 g/dl; AST, 18 U/l; ALT, 9 U/l; GGT 20 U/l; ALP 111 U/l; amylase 40 U/l; total bilirubin 1.47 mg/dl; FSH 52.62 mIU/ml; LH 23.11 mIU/ml; total testosterone 3.28 ng/ml; oestradiol 21.59 pg/ml. An abdominal ultrasound scan showed 23 mm anechoic, saccular expansion in the left branch of portal vein. There were no features of thrombosis, portal hypertension, chronic liver disease, pancreatic mass or pancreatitis. No aneurysmal change was noted in arterial tree and there were no pathological findings in other intraabdominal organs. Monophasic, turbulent venous flow was detected in aneurysmal dilatation by Doppler ultrasonography. Esophagogastroduodenoscopy was performed and revealed pan gastritis. Abdominal pain was attributed to gastritis.

Conclusion

Portal vein aneurysms are rare presentations and are usually asymptomatic. Portal vein thrombosis is a severe complication of PVA and can result in intestinal ischemia or intestinal infarction. Early diagnosis and initiation of therapy is important. It is well known that KS is associated with an increased risk of venous thromboembolism including portal vein thrombosis. So, it is important to follow up the patient for the risk of portal vein thrombosis. For asymptomatic patients regular clinic follow-up will be sufficient.

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EP1202

Exaggerated cortisol response in heterozygous carriers with a mutation in the melanocortin-2 receptor (MC2R) gene

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Introduction

Familial glucocorticoid deficiency (FGD) is a rare autosomal recessive disease characterised by ACTH resistance and isolated glucocorticoid deficiency. Mutations of ACTH receptor, known as melanocortin-2 receptor (MC2R), and melanocortin-2 receptor accessory protein (MRAP) account for approximately 25 and 15 to 20% of cases respectively. To date there is no strong evidence that heterozygous carriers have abnormal cortisol secretion.

Case report

We studied a pedigree with a MC2R mutation where the index case presented with severe hypoglycaemia at three years of age in 1970s and was subsequently diagnosed with adrenal insufficiency. Of eight siblings, two brothers died as neonates, with hindsight due to adrenal insufficiency and a third brother was diagnosed with adrenal insufficiency when he presented comatose at two months and remained profoundly handicapped and later died. The index case was found to have a homozygous missense mutation c.221G>T, leading to p.S74I (substitution of serine with isoleucine at position 74) in the MC2R gene. We studied three of her siblings with the heterozygous S74I mutation in the MC2R gene. The mean age of heterozygous carriers was 31.3 ± 2.5 years. They had generalised slightly tanned skin, but no significant hyperpigmentation. They were normotensive and had no symptoms suggestive of glucocorticoid deficiency. Short synacthen testing with 250 μg tetraoctactide in heterozygous carriers showed baseline ACTH levels of 53.7 ± 31.9 ng/l (normal range < 46 ng/l). 0 min cortisol levels of 506 ± 168 nmol/l, 30 min cortisol levels of 952 ± 85 nmol/l, and 60 min cortisol levels of 953 ± 36 nmol/l.

Conclusion

The study of heterozygous MC2R mutation carriers demonstrated slightly elevated baseline ACTH levels with a relatively high baseline cortisol level and an exaggerated cortisol response to synacthen test. These findings suggest there is no evidence of glucocorticoid deficiency despite elevated ACTH levels in heterozygous carriers with MC2R mutations.

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EP1203

Pituitary enlargement in pregnancy presenting with visual field defects and interesting imaging

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We report a rare case of a patient presenting with headaches and almost complete bilateral hemianopia during her third trimester of pregnancy. This lady presented with headaches and vomiting 2 years prior, with a pituitary MRI initially reporting an acute pituitary haemorrhage. This time, due to progression of her visual field defects, it was decided in a multidisciplinary meeting to perform a Caesarean section at 37 weeks and start Cabergoline post-operatively, as the patient did not plan to breast-feed. She had a raised prolactin in keeping with pregnancy, but the rest of her pituitary profile was normal. Upon reviewing her initial pituitary MRI and subsequent imaging at a later date, it was noted that the patient had a bulky pituitary gland, but the signal characteristics on MRI remained unchanged, which brought the original diagnosis of pituitary haemorrhage into question. It was therefore felt that this was either a proteinaceous developmental cyst or persisting blood products on serial imaging. This pituitary abnormality in combination with physiological pituitary gland enlargement in pregnancy is likely to have caused chiasmal compromise and visual field defects in this patient. Since her delivery, she has had repeat MRI imaging, which showed regression in the size of her pituitary gland with no compression of the optic chiasm. She was gradually weaned off the cabergoline. There is no evidence of any endocrine dysfunction. However, the patient still reports some persisting visual defects, which are unaccounted for in view of her most recent pituitary imaging. She has been referred on for neuro-ophthalmic assessment. This case also demonstrates the importance of multi-specialty management in a complex patient to achieve a satisfactory outcome. The patient has been strongly advised to avoid future pregnancies, as it is likely that she will get chiasmal compression once again.

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EP1204
Familial SDHC mutation associated with prolactin/growth hormone-secreting pituitary adenoma and paraganglioma
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Introduction
SDH genes mutations are associated with hereditary phaeochromocytoma and paraganglioma syndromes. We describe the case of a patient with SDHC related familial paraganglioma and pituitary adenoma.

Case
A 65-year old man consulted for an incidentally discovered 7 cm abdominal mass on CT-scan, lateral to the right kidney, invading inferior vena cava, associated to a retroperitoneal adenomegaly and a lesion on the lobe of L2 vertebral with spinal MRI aspect of metastasis. All these lesions showed hypermetabolism on 18F-FDG PET. Continuous blood pressure monitoring, plasma catecholamines and their methoxylated metabolites were normal. Chromogranine A was four times normal (Normal range (100 µg/l). Total right adrenalectomy, lumbo-aortic lymphadenectomy and nephrectomy were performed. Vertebral metastasis was treated by radiofrequency. Histopathology of the primary tumor confirmed the diagnosis of paraganglioma with 2% mitotic index. During follow-up, erectile dysfunction developed. Endocrine evaluation revealed partial hypogonadotropic hypogonadism (testosterone 214 ng/dl Normal: (280–820), LH 2.2 mUI/ml, FSH 1.7 mUI/ml). GH and IGF1 were 6.6 ng/dl and 318 ng/ml. GH and IGF1 were 10.31 ng/ml and 861 ng/ml. 75gOGTT did not suppress GH (nadir GH: 10.26 ng/ml). MRI demonstrated a pituitary adenoma of 18 × 19 mm with left cavernous sinus extension without optic compression. We retained the diagnosis of PRL/GH-secreting pituitary adenoma and started treatment by radiofrequency.

Conclusion
This case suggests that SDHC gene mutations could be related to pituitary adenomas occurrence in association with paraganglioma syndromes, but more studies should be conducted to define the pathogenic pathways of this relationship.

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EP1205
Bilaterally slipped capital femoral epiphysis in growth hormone–deficient patient: osteosynthesis also needs the oestrogen oestrogenic fusion-case report
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Introduction
Growth without growth hormone is seen also in patient with craniohypophyngia. We just speculate what anabolic factors might be involved in this process. However, oestrogen through its receptors lead to epiphyseal fusion. In this case report we would like to present the patient with bilateral slipped femoral epiphysis (SFE) and interventions made at tertiary health care level.

Case Report
20-years-old female, operated from craniohypophyngia when was 10 year, body height 167 cm, body weight 71.8 kg, not regularly on levotheroxine 50 gr, in December 2013 presented as pain in right hip, on X-ray SFE, and osteosynthesis was performed. In July 2013 similar clinical picture but on left side. Patient was send at tertiary level. After multislice CT scanning same surgical procedure performed on left femur with three screws. Then patient was moved on endocrinology department. Clinically, according to sex characteristics, patient was Tanner I stage, without measurable values of growth hormone, insulin like growth factor I, gonadotropins and estrogens, insulinaemia 17.3 mU/ml, blood glucose 4.5 mmol/l. On X-ray of the left hand skeletal age was 12 year. Estrogen therapy started with 0. mg etinil estradiol and after 5 months increased on 2 mg estradiol, 21 and 7 days pause. Skeletal age at 12 was 8 years 6 months, 14 years, 15–16 years respectively. Increased markers of bone resorption (cross laps) returned back into normal range. DEXA scan of lumbar spine was improved from –3.2 T-score onto –2.8 in just 6 month period. Body height was changed from 167.5 cm to on 171 cm and body weight from 67.5–80 kg.

Conclusions
After the operation of craniohypophyngia and growth without growth hormone we have to follow skeletal growth and on time introduce sex hormones. Later, in young adults we have to consider a small dosages of growth hormone to improve their body composition.

EP1206
Effectiveness of octreotide administration before surgery for GH-TSH co-secretting pituitary adenoma with thyrotoxicosis: a case report
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Introduction
TSH-secreting pituitary adenoma (TSHoma) sometimes brings on rare cause of hyperthyroidism because of its excessive TSH secretion. Though the first line of treatment for TSHoma is surgical removal of tumour, hyperthyroidism often causes perioperative thyroid storm. Here, we report a case of GH-TSH pituitary adenoma whose thyrotoxicosis was controlled by 5 days’ octreotide (OCT) subcutaneous administration before surgery.

Case Report
A 47-year-old woman with hyperhidrosis and palpitation for these 7 years was admitted to our hospital. She also presented acromegalic change, such as the increase in size of finger rings and shoes. In endocrinological examination, serum levels of TSH, fT 4 and fT3 were 1.50 mU/l, 3.73 ng/dl and 8.06 pg/ml, and LH and IGF1 were 10.31 ng/ml and 861 ng/ml. 75gOGTT did not suppress GH (nadir GH: 10.26 ng/ml). MRI demonstrated a pituitary adenoma of 18 × 19 × 9 mm. GH-TSH co-secretting pituitary adenoma was suspected, and in order to prevent from perioperative thyroid storm, we scheduled OCT administration. Single OCT administration (50 µg) decreased serum TSH levels from 1.740 to 0.515 µU/ml and GH levels from 11.42 to 0.68 ng/dl respectively. Then, OCT administration was injected additionally for 5 days and serum fT 4, fT3 and IGF1 levels decreased to 1.53 ng/dl, 2.65 pg/ml, and 350 ng/ml respectively after operation. Pituitary adenoma was completely and unevenly moved via trans-sphenoidal-surgery and her all hormone levels were normalized without any medication.

Conclusion
A case of GH TSH co-secretting pituitary adenoma with thyrotoxicosis was reported. To prevent from perioperative thyroid storm, OCT administration should be recommended.

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Cushing's syndrome secondary to aberrant hormone receptors in a patient with macronodular adrenal hyperplasia ACTH-independent

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Introduction
Cushing's syndrome (CS) due to macronodular adrenal hyperplasia ACTH-independent (MAHAI) is rare. Regulation of cortisol secretion by G-protein-coupled receptors (GPCRs) aberrantly expressed is frequently found in MAHAI. Various aberrant receptors have been reported, mostly: GIP, vasopressin, beta-adrenergic, LH/ICG and serotonin.

Case report
61 years old woman. Medical history: type 2 diabetes, hypertension, obesity, dyslipidaemia and severe sleep apnoea. Treatment: metformin, insulin, lyxisenatide, irbesartan-hydrochlorothiazide, torasemide, diltiazem, acetyl salicylic acid and atorvastatin. Physical examination: moon face, centripetal obesity, abdominal striae and thin extremities. Laboratory evaluation: HbA1c 8.4%. TSH 2.06 µU/ml, serum cortisol: at 0800 h: 17.2 µg/dl (5–25), overnight dexamethasone suppression (1 mg): 5.3 µg/dl, after 0.5 mg dexamethasone every 6 h for 48 h suppression: 5.03 µg/dl, after nocturnal 8 mg dexamethasone suppression: 5.7 µg/dl. Urinary free cortisol repeatedly normal (49.4 and 24 µg per day), salivary cortisol repeatedly raised (0.382 and 0.292 ng/ml). ACTH 2.83, others adrenal hormonal profile normal. With these findings, the suspected diagnosis was Cushing's syndrome. CT: adrenal glands enlarged with homogeneuos hypodense nodules (3.3 x 2.6 cm right; 3.2 x 1.9 cm left). Because of the known association between MAHAI and aberrant GPCRs some tests were performed: posture test, standard mixed test, LHRII (100 mg i.v.), metoclopramide (10 mg orally), glucagon (1 mg i.v.) and AVP (10 IU i.m.). Positive response (50% increase in plasma cortisol levels) in the standard mixed test and metoclopramide test (indicating serotonin and GIP aberrant receptors). Right adrenalectomy was planned.

Conclusion
In patients with MAHAI aberrant GPCRs can be identified. The detection of such aberrant receptors is necessary in all patients with MAHAI. Identification of these receptors can provide specific pharmacological treatment with or without adrenalectomy.

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Complicated investigation of adrenal incidentaloma in a critically ill patient – a case report

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Adrenal incidentaloma is frequently encountered in endocrinological praxis, however in specific situations the proper investigation is almost impossible. A 60-years old patient was admitted to our intensive care unit with a myocardial infarction in cardiogenic shock requiring ionotropic support and intraaortic balloon counterpulsation. On account of ejection fraction 15–20% an urgent pretransplantation investigation was started. Abdominal ultrasound displayed a hypoechogenic structure 35 x 37 mm in the left supra renal area and adrenal CT confirmed a low density mass 25 x 37 mm. Both aldosterone (886.8 ng/l) and plasmatic renin activity (PRA) (5.9 ng/ml/h) were highly elevated but our patient was treated with interfering medication (furosemide and spironolactone). Plasma metanephrine levels were within normal limits despite of catecholamine hypersecretion. The patient had no cushingoid features and ACTH level was normal, but plasma cortisol and testosterone levels were normal. Hepatitis B, C, HIV and anti nuclear antibodies were negative. Chest X-ray and abdominal ultrasound were normal. Psychiatrist excluded a psychiatric disorder. Standard and 1 µg Synacthen test showed inadequate peak cortisol 419 and 532 nmol/l respectively. Insulin tolerance test, with hypoglycaemia of 1.2 mmol/l in 30’, showed inadequate peak responses of ACTH 25 ng/l in 30’, cortisol 345 nmol/l in 60’, prolactin 282 mU/l and low normal growth hormone 22 mU/l in 60’. Endocrinology with hypopitathalamic-pituitary region MRI was normal. The patient was diagnosed with chronic fatigue syndrome (CFS). As we advised he stopped working in shifts and commenced a low-grade physical activity with cognitive – behavioural therapy. After 6 months he was complaint free with adequate cortisol levels in standard and 1 µg Synacthen test, 718 and 715 nmol/l respectively. After a year he was still complaint free with basal cortisol 570 nmol/l.

Conclusion
The cause of CFS in our patient was the long-term exposure to a stressor – shift work, which led to a circadian disruption, crashing adaptive mechanisms and leading to a disease.

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A case of pleomorphic adenoma and acromegaly: a coincidence or a pathophysiological association?

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Introduction
Acromegaly is a chronic disease caused by excessive secretion of growth hormone (GH), and as a result, of insulin-like growth factor-1 (IGF1). Although controversial, frequency of both benign and malignant neoplasm formation is thought to be increased in acromegalic patients. Pleomorphic adenoma is the most
common arising tumour from the parotid salivary gland. Here we report the case of a 33-year-old woman with acromegaly and also who presented with a swelling on the left neck and diagnosed as pleomorphic adenoma arising from parotid gland after excision of the tumour.

Case report

33-year-old woman admitted to the hospital complaining of a 2-week history of visual loss and headache. She also determined weight gain, menstrual irregularity, libido loss, galactorrhoea, and a slowly growing swelling on the left neck during the last year. Hypophysal MRI revealed a mass of 20x32 mm occupying the sella and invading right cavernous sistaernae and extending to the optic chiasma. Hormonal evaluation demonstrated that the patient had acromegaly and secondary hypothyroidism. Parotid ultrasound (US) revealed a 42x28x45 mm heterogeneous, hypoechoic intraglandual lobulated solid mass occupying left parotid gland superficial lobes and extending to the deep lobe. Hypophysal adenoma was excised by transphenoidal route and immunohistochemical analysis showed extensive GH positivity. She had residual tumour after the operation and somatostatin analogous therapy was started in the follow-up period. After eight months from the hypophyseal operation the parotid tumour was excised and pathology showed that it was a pleomorphic adenoma.

Conclusion

It seems that this is the first case of a coincidence between an acromegaly and pleomorphic adenoma of parotid gland in the English literature. We don’t have still enough knowledge about an association between salivary gland tumours and acromegaly. If present or not this association must be evaluated with the further studies.

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Primary hyperaldosteronism: case presentation

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Introduction

We should consider testing for primary aldosteronism in the presence of hypertension and hypokalaemia, resistant hypertension, onset of hypertension at a young age (<20 years), severe hypertension and whenever considering secondary hypertension.

Case report

We presented the case of a 38 years old woman who was admitted in the National Institute of Endocrinology C.I. Parhon Bucharest for the evaluation of high blood pressure. She has high blood pressure for 10 years (maximum value 190/100 mm/Hg) and she is on β blocker and angiotensin II receptor blockers. She has no other medical history and her blood pressure is still 150/80 mm/Hg on the antihypertensive drugs. She has heredodepartal antecedents of high blood pressure (her mother). After she has stopped for 4 weeks the antihypertensive drugs, we detected hypotopasemia (K: 2.9 mmol/l), normal serum natrium, and normal biochima but high levels of serum aldosterone (121 ng/ml) and low levels of serum renin (2 μεg/ml) with plasma metanephrines and normetaneophepine in the upper normal range and normal plasma cortisol with good response after 1 mg overnight dexamethasone suppression test. An adrenal computed tomography has been performed and we discovered a left adrenal mass of 1.2x0.9 cm. We have replaced the β blocker with Spironolactona (200 mg per day) and Asparacardin and on these medications she has high normal blood pressure and normal potassium. The patient was transferred to the surgery where they performed laparoscopic adrenalectomy. 2 weeks after surgery she has normal blood pressure and normal natriaemia and potassium without medications.

Conclusion

We presented the case of woman with primary hyperaldosteronism and although she has high blood pressure for 10 years and we have not expected that it would be entirely corrected after surgery, patient did not need any antihypertensive drugs after surgery.

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Hyperprolactinaemia and breast abscess: is there a link?

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Introduction

Hyperprolactinaemia is a common endocrine condition causing galactorrhea. Breast abscess is a frequent complication of the post partum period and breast feeding but it rarely occurs out of these two situations. We report the case of a patient presenting with tumoural hyperprolactinaemia associated with a breast abscess.

Case report

A 34 years-old patient presented with galactorrrhea, spiniomenorrheoa and headache for six months. She had nothing special in her medical history and was not on drugs. She was the mother of two children aged eight and four. Prolactina assessment was made twice and confirmed the hyperprolactinaemia (Prolactine: 94 and 110 ng/ml). Pituitary MRI concluded to a pituitary microadenoma so that microprolactinoma was diagnosed and the patient put on dopaminergic agonists. 15 days later, the patient suddenly developed a painful mass of the left breast. Biologic assessment showed an inflammatory syndrome with hyperleucocytosis. The breast ultrasound examination revealed an abscess of 4 cm in the superior external quadrant, with no other abnormalities of the breast. The course of the abscess was good on antibiotics (Amoxicillin + clavulanic acid) and surgery was not indicated.

Conclusion

This case report highlights the fact that during pathological hyperprolactinaemia, the histology of the breast glands may be modified leading to a risk of developing breast abscess. This phenomenon is may be exactly the same than during breastfeeding. No other similar cases have been reported in the literature.

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5 years complete clinical remission after single adrenalectomy for severe occult ACTH-dependent Cushing’s syndrome

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Introduction

Complete long-term clinical remission in occult ectopic ACTH syndrome after a single adrenalectomy is unexpected.

Case report

5 years ago, a 54-year-old man was admitted because of resistant HTA, multiple severe vertebral fractures, muscle weakness and cushingoid features of at least 1 year. Adrenal tests were diagnostic of ACTH-dependent Cushing syndrome: ACTH=263 pg/ml, high plasma (62 μg/dl) and urinary free cortisol (UFC=1256 μg per day) with no suppression after both low-dose (cortisol=40.12 μg/dl; UFC=255.36 μg per day) and high-dose dexamethasone (cortisol=32.95 μg/dl; UFC=199.2 μg per day). A pituitary MRI showed no identifiable tumour. CTS of the thorax and abdomen and a 18-FDG-PET CT scan failed to identify a possible tumour. A right adrenal laparoscopic adrenalectomy was performed. 1 mo post surgery ACTH decreased to 79.8 pg/ml and cortisol was 16.7 μg/dl, non-suppressible with low dose DXM (7.37 μg/ml); low testosterone, 25OHD normalized, and bone turnover markers increased significantly (osteocalcin 10 X). As clinical improvement was significant the patient declined the second adrenalectomy. 10 mo post surgery all cushingoid features disappeared and the patient was in very good clinical condition with mild HTA and normal blood chemistries as he is now. Adrenal tests were performed annually: they fluctuated, with serum cortisol/UFC normal or high normal but nonsuppressible (or paradoxically increased); ACTH also was around 100 pg/ml. In the next year, a CT scan revealed a small pulmonary nodule (10 mm) but a SMS (111-indium-pentetreotide) scan was negative; the nodule was stable on recent CT. We wait for the patient consent to operate the pulmonary nodule.

Conclusion

This case shows an unexpected rapid and complete clinical remission of a severe occult ectopic Cushing’ syndrome. The abnormal cortisol feed-back persisted for the duration of follow-up.

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Introduction

A 24-year-old female was referred for evaluation of severe hypertension associated with hypokalaemia. Primary aldosteronism with concurrent subclinical Cushing’s syndrome was diagnosed. A CT-scan identified a lesion of 4 cm in the right adrenal gland and a second lesion of 1 cm in the left adrenal gland, both displaying benign imaging phenotype. Following dexamethasone suppression, we explored the potential aberrant expression of serotonin receptors in the adrenal cortex by intravenous administration of metoclopramide, a serotonin type 4 receptor (5-HT4-R) agonist. This led to abnormal cortisol increase and physiological response of aldosterone in peripheral blood. Adrenal venous sampling was then performed in basal conditions and after metoclopramide stimulation. An increase in cortisol level was observed in the left adrenal vein after stimulation. 131I-19-Iodocholesterol scintigraphy showed intense radiotracer uptake in the right adrenal mass and weak uptake in the contralateral mass. Right laparoscopic adrenalectomy was performed. Histological examination revealed 5-HT4-R antagonist GR113808. Incubation of tumour tissue fragments with 5-HT induced a significant increase in aldosterone production which was absent in the progesterone tissue. This suggests that 5-HT4 receptors expression of 5HT4 receptors.

In vitro studies revealed enhanced sensitivity of the tumour tissue to 5-HT4-R agonistic of illicic expression of 5HT4-R receptors. We report a rare case of an aldosterone- and cortisol-co-producing adenoma in a patient with severe hypertension and bilateral adrenal masses exhibiting an abnormal plasma cortisol response to metoclopramide. In vitro studies revealed enhanced sensitivity of the tumour tissue to 5-HT4-R agonistic of illicic expression of 5HT4-R receptors.

Conclusion

We report a rare case of an aldosterone- and cortisol-co-producing adenoma in a patient with severe hypertension and bilateral adrenal masses exhibiting an abnormal plasma cortisol response to metoclopramide. In vitro studies revealed enhanced sensitivity of the tumour tissue to 5-HT4-R agonistic of illicic expression of 5HT4-R receptors.

Conclusion

We report a rare case of an aldosterone- and cortisol-co-producing adenoma in a patient with severe hypertension and bilateral adrenal masses exhibiting an abnormal plasma cortisol response to metoclopramide. In vitro studies revealed enhanced sensitivity of the tumour tissue to 5-HT4-R agonistic of illicic expression of 5HT4-R receptors.

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Introduction
Phaeochromocytoma in pregnancy is very rare and potentially dangerous situation for mother and foetus. Failure to diagnose this condition or suboptimal management can be disastrous for mother and/or foetus, because of raised catecholamine levels.

Case
A 22-year-old pregnant woman (8 weeks’ gestation) with hypertension and a suspected recurrence of phaeochromocytoma was referred to the Endocrinology Department in March 2014. The pregnancy was unplanned. In physical examination her height – 176 cm, weight – 74 kg, blood pressure and pulse were 156/90 mmHg and 92 beats/min respectively. Laboratory investigations: metanephrine 0.42 nmol/l (0–0.456), normetanephrine > 16.38 nmol/l (0–1.037), potassium 3.4 mmol/l (3.6–5.3), plasma renin activity (PRA) 16.81 ng/ml (1.6–14.7), aldosterone (ALD) 633 ng/l (35–300), with normal ALD:PRA ratio, chromogranin A 361.18 µg/l (0–100). From her medical history it was already known that she underwent right adrenalectomy due to pheochromocytoma in March 2012. 6 months later increased blood pressure till 160/100 mmHg was known that she underwent right adrenalectomy due to pheochromocytoma in March 2012. 6 months later increased blood pressure till 160/100 mmHg was observed. On abdominal CT scan (June 2013) – right adrenal gland removed, several ~1.1 × 1.0 cm lymph nodes are visible, left adrenal gland structural, without any additional masses in it. Metanephrin and normetanephrin tests indicated significantly elevated catecholamines levels. Unfortunately abdominal MRI (August 2013, September 2014) and MIBG scans (October 2013, February 2014) did not reveal possible source of catecholamines hyperproduction as well. Genetic testing results were negative. Hypertension during first trimester was treated with Labetalol 60mg/day, Metildopa 1000 mg per day, potassium chloride 1500 mg per day. Phenoxybenzamine hydrochloride was added later on and titrated till 100 mg per day in order to reach satisfactory blood pressure control. In September 2014 the patient had uncomplicated delivery of a healthy boy (weight – 2890 g, height – 47 cm, Apgar score 9–9) via Caesarean section. She is breast-feeding and continues Labetalol 900 mg per day for hypertension control. Further investigations are planned to identify localization of phaeochromocytoma.

Conclusion
This case illustrates that adequate medical management in the case of phaeochromocytoma predispose the successful pregnancy outcome.

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EP1218
Rare aetiology for primary adrenal failure: ACTH resistance
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Introduction
ACTH resistance syndromes are rare, autosomal and genetically heterogeneous diseases that include familial glucocorticoid deficiency and triple A syndrome. ACTH resistance syndromes are rare, autosomal and genetically heterogeneous diseases that include familial glucocorticoid deficiency and triple A syndrome. These are characterised by early onset of primary adrenocortical insufficiency associated with hypoglycaemia, convulsions and skin pigmentation.

Case report
We present the case of primary adrenal failure in a boy diagnosed at the age of four, during a decompensation episode with hypoglycaemia and hyponatremic convulsive episode. Adrenal functional evaluation revealed: cortisol 17.6 ng/dl and very high Z-scores were objectified. To the clinical and biologic status (normal natremia and glycaemia). The aetiological evaluation for this adrenal insufficiency included: negative anti-adrenal antibodies, normal long chain fatty acids, negative tuberculosis testing, normal 17-OH progesterone and normal pituitary (McR) and normal adrenal aspect (CT). This profile suggests a possible diagnosis of ACTH resistance syndrome. Molecular analysis for the ACTH receptor gene (MC2R) and its associated protein (MRAP) is needed for confirming this diagnosis. Clinical aspect is particular: no skin hypopigmentation (high ACTH > 1500 pg/ml). Glucocorticoid and mineralocorticoid treatment improved the clinical and biologic status (normal natremia and glycaemia). The aetiological evaluation for this adrenal insufficiency included: negative anti-adrenal antibodies, normal long chain fatty acids, negative tuberculosis testing, normal 17-OH progesterone and normal pituitary (McR) and normal adrenal aspect (CT). This profile suggests a possible diagnosis of ACTH resistance syndrome. Molecular analysis for the ACTH receptor gene (MC2R) and its associated protein (MRAP) is needed for confirming this diagnosis. Clinical aspect is particular: no skin hypopigmentation (high ACTH > 1500 pg/ml) suggesting a possible melanocyte receptor deficiency (MC1-R). This ACTH resistance diagnosis seems to be associated with alacrima (Shirmer test confirmed low lacrimal secretion) but no achalasia symptoms were objectified.

Discussion
Several mutations have been found to affect the ACTH-R gene and results in different effects on receptor function. Given the ACTH resistance on multiple receptor locations: MC1-R, MC2-R (adrenal insufficiency, absence of hyperpigmentation) we suspect a co-factor mutation. Molecular analysis of DNA for MC2R, MRAP, and AAAS genes in literature shows that about 50% of FGD has unknown genetic cause. Recently, it was shown that MC2R interacts with Nup50, a nuclear pore complex protein, suggesting that this interaction could be a novel mechanism of action of ACTH receptor.

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EP1219
Autoimmune hypophysitis: from pituitary expansion to empty sella: description of four cases
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Four patients with autoimmune hypophysitis were followed since the diagnosis of the disease. All presented with severe headache, decreased libido, astenia. Case 1 and 3 presented polyuria and polydipsia. At MRI pituitary was enlarged, with high gadolinium uptake and stalk enlargement.

Case 1, male 41 years. MRI volume: AP 13 mm, CC 7 mm. Hormonal assessment: central hypothyroidism, hypoadrenalism, hypogonadism, normal GH and IGF1, hyperprolactinemia, central diabetes insipidus. Pituitary biopsy: severe lymphomonocytic infiltrate. Case 2, male 54 years. MRI volume: AP 13.5 mm, CC 7.7 mm. Hormonal assessment: central hypothyroidism, hypoadrenalism, GH deficiency, hyperprolactinemia. Case 3, male 74 years. MRI volume: AP 9 mm, CC 7 mm. Hormonal assessment: panhypopituitarism, central diabetes insipidus. Pituitary biopsy: rich IgG4 lymphomonocytic infiltration. Case 4, female 35 years. MRI volume: AP 16 mm, CC 7 mm. Hormonal assessment: panhypopituitarism, hyperprolactinemia. All patients were treated by oral prednisone therapy (starting dose: 40 mg/day gradually tapered over 6 months) and followed with regular hormonal exams and pituitary MRI. At the last outpatient visit: Case 1 (6 years AR): recovery of gonadic and thyroid function, GH deficiency, adrenal insufficiency and diabetes insipidus remained unchanged. MRI: shrinked pituitary (AP 8 mm, CC 4 mm). Case 2 (1 year AR): complete recovery of adrenal function, persistence of hypogonadism and GH deficiency, subclinical hypothyroidism. MRI: shrinked pituitary (AP 11 mm, CC 2.5 mm). Case 3 (6 years AR) persistence of panhypopituitarism and diabetes insipidus. MRI: shrinked pituitary (AP 6 mm, CC 4 mm). Case 4 (1 year AR) complete recovery of pituitary function. MRI: normal pituitary volume (AP 12 mm, CC 4 mm). Conclusion
Glucocorticoid treatment is effective in improving pituitary function and pituitary mass. Over the years new hormonal defects may appear along with pituitary shrinkage: empty sella might be the outcome of autoimmune hypophysitis. (abbreviations: AR, after remission; AP, antero–posterior diameter; CC, crano-caudal diameter).

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EP1220
Occurrence of liver failure in post-surgery hypopituitaric patients
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Multiple pituitary hormone deficiency and hypothalamic obesity are common complications after brain surgery for childhood tumors. Despite adequate replacement hormone therapy, obesity develops equally, but liver failure is not usually described. In this study, four subjects who had undergone surgery for brain tumors involving the peri-hypothalamic area when they were nursing or as youths (9 months, 6 years, 9 years and 20 years). They were referred to our Unit when they were 19, 23. 23 and 31 years, respectively. One of these patients had a pilocytic astrocytoma, two of these patients had a craniopharyngioma, and the last a third ventricle germinoma. One patient underwent radiotherapy and
chemotherapy after surgery and another one received four tranphenoidal or transcranial surgical operations. All patients developed panhypopituitarism, but only two had taken in childhood and adolescent age adequate hormone replacement therapies since brain damage. Since the other two patients came to our observation, adequate hormonal replacement therapy was proposed. All patients developed obesity (BMI 39.2–46.6 kg/m²) or overweight (BMI: 27.1). The two patients adequately treated for hypopituitarism after surgery, developed a fatty liver when they were 16 and 21 years old respectively. In both cases, steatosis progressively evolved into cirrhosis after 2 years. One of these patients also developed a hepatic-pulmonary syndrome and underwent liver transplant at the age of 25 years. In the two patients with inadequate or absent hormone replacement therapy, a diagnosis of cirrhosis was concomitant with the first appropriate endocrinological care during hospitalization for liver failure. The analysis of these four cases shows that pediatric peri-hypothalamic surgery may be associated with very severe hepatic clinical features, induced by mechanisms not yet known, regardless of hormone replacement therapy. It is therefore very important to start a careful follow-up of these patients from childhood for early detection of possible liver failure.

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**EP1222**

**Glucocorticoid resistance syndrome: case report**

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Introduction

Glucocorticoid resistance syndrome (GRS) is a rare familial or sporadic condition, caused by mutations in glucocorticoid receptor gene. It is characterised by generalised partial resistance of target tissues to cortisol action and compensatory elevation of ACTH with subsequent hyposecretion of cortisol, mineralocorticoids and androgens. Its clinical spectrum is broad and it may occur with high blood pressure (HBP) metabolic alkalosis, hypokalaemia and virilisation.

Case report

A 19-year-old black male was referred to Endocrinology department due to HBP diagnosed at 14 years old and elevated ACTH. He had delayed psychomotor development and epilepsy since childhood. There was no history of precocious puberty. His height, weight and blood pressure were 1.70 m, 52 kg and 139/95 mmHg, respectively. No signs or symptoms of deficiency or excess of glucocorticoids, hyperandrogenism or other causes of HBP were present.

Complementary exams excluded adrenal enzymatic deficiency, primary aldosteronism, phaeochromocytoma and renovascular disease as aetiology of HBP. Pituitary–adrenal axis evaluation revealed: ACTH 158 pg/ml (ND-46), cortisol(s) 08/24 h 21.9/1.8 μg/dl, cortisol (u) 102.5 μg/24 h (20–90); low-dose dexamethasone suppression test (DST): cortisol(s) 19.8 μg/dl; high-dose DST: cortisol(s) <1.0 μg/dl. DNA analysis revealed a frameshift mutation c.2159_2160delAA, in heterozigoty in the NR3C1 gene, not yet described in the literature. Genetic study of relatives has not been done yet, since they live abroad.

Conclusions

The clinical spectrum of GRS is broad, ranging from severe to asymptomatic forms and the biochemical profile varies, depending on the severity of the defect in the signal transduction of glucocorticoids. Persistent elevated urinary cortisol and ACTH with no clinical signs of hypercortisolism in this hypertensive young man led us to suspect of GRS. Diagnosis was confirmed by the finding of a not yet described mutation of NR3C1 gene.

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**EP1223**

**Bilateral adrenal haemorrhage: a rare complication of anti phospholipid syndrome**

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Introduction

Bilateral adrenal haemorrhage is a rare potentially life-threatening event that occurs either in traumatic or non traumatic conditions. We present a rare case report of bilateral adrenal haemorrhage due to anti-phospholipid antibody syndrome.

Case report

A 54 year old Iranian origin male presented with abdominal pain and collapse. His past history includes unprovoked DVT 6 months ago and off the warfarin recently. CT abdomen showed bilateral Adrenal haemorrhage. Early morning cortisol was 54. He was subsequently treated with i.v. hydrocortisone, antibiotics, fluids and made a good recovery. He had further admission within 1 week of discharge with chest pain and hypotension due to acute myocardial infarction. Coronary artery angiogram was normal. Further investigation showed positive ANA and lupus anticoagulant positive. He was discharged on oral hydrocortisone and warfarin. The diagnosis of anti phospholipid antibody syndrome was confirmed after repeat lupus anticoagulant positive at 3 months with satisfactory clinical and biochemical criteria.

Discussion and conclusion

Acute adrenal insufficiency due to bilateral adrenal haemorrhage is a rare manifestation of APS. Prompt treatment with steroids needed to achieve favourable outcome.

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EP1224
Cushing's disease in a patient with complicated varicella
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Introduction
Immunosuppression is a possible consequence of hypercortisolism, putting these patients in a state of increased risk of infections.
Case report
Female, 19 years old. In July 2014 she seek for medical care because she became febrile and developed an erythematous rash on her face/trunk with subsequent widespread to the entire body. She was admitted in the ICU with the diagnosis of severe varicella with acute cholestatic hepatitis and confluent necrosis of coagulative type. The patient presented full moon face (more prominent over the last 2 months), truncal obesity starting after menarche (at 10 years old), hirsutism and menstrual irregularities/secondary amenorrhea. Physical examination also showed bruises and reddish purple striae. During hospitalisation she presented hypertension, hyperglycaemia (HbA1c 6.7%) and hypokalaemia. After treatment with antiviral/antibacterial drugs and the resolution of the acute infection, she was evaluated for the suspicion of Cushing’s syndrome, which was confirmed based on: high levels of serum cortisol; high 24 h urine free cortisol (300.1 μg/day); two increased late-night salivary cortisol assays (1.150 μg/dl; 0.961 μg/dl); cortisol after 1-mg overnight dexamethasone suppression test (DST) – 23.0 μg/dl; and cortisol after 2 day low-dose DST – 15.1 μg/dl. As she had high basal ACTH levels (14.7 μg/ml), it was performed a 2 day high-dose DST test (end cortisol – 3.8 μg/ml). Then it was performed a pituitary MRT, which reveals a ‘lesion in the right half of the pituitary gland compatible with a microadenoma’, thus confirming the diagnosis of Cushing’s disease.

Discussion
This clinical case emphasizes the importance of considering hypercortisolism as a condition capable of inducing immunosuppression, which may result in the development of serious infections and, therefore, these severe clinical situations should raise this diagnostic possibility.

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EP1225
Anaesthesia during petrosal sinus sampling and possible interference with ACTH levels
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Background
General anaesthesia and surgical intervention in humans are known to affect the function of the hypothalamic–pituitary–adrenal axis (HPA). In the literature there are conflicting reports about the effect of propofol, a commonly used intravenous anaesthetic agent, on HPA function.

Case reports
We report two males (11 and 12 years) with ACTH-dependent Cushing syndrome (CS) who underwent inferior petrosal sinus sampling (IPSS) with general anaesthesia. ACTH was measured from bilateral petrosal and peripheral sites at baseline and after administration of corticotropin releasing hormone (CRH). Anaesthetic agents used included: propofol infusion (pt A: 7.8 mg/kg; pt B: 29 mg/kg), fentanyl, and midazolam. ACTH results from IPSS were atypical for both patients (i.e. no stimulation of ACTH (peripherally) and overall low values of ACTH). Since the ACTH results precluded scheduling of transsphenoidal surgery, the IPSS procedures were repeated. Results of the 2nd IPSS showed appropriate stimulation of peripheral and central ACTH levels and peripheral to central ratios consistent with Cushing disease (CD) in both patients. Anaesthetic agents used included single dose propofol at induction (~ 50 min prior to sampling) (pt A: 1.8 mg/kg; pt B: 1.4 mg/kg), fentanyl, and midazolam. Subsequently, both patients underwent TSS for removal of corticotropinoma which was confirmed at histology; they remain in remission of hypercortisolemia to date.

Conclusion
Historically, propofol has been shown to have direct antisteroidogenic effects on adrenal cells and to be a weak inhibitor of adrenal steroidogenesis, compared to etomidate. However, the two cases presented provide a novel insight about a possible interaction of propofol and ACTH. These cases suggest a possible short-term inhibition of ACTH secretion by propofol and highlight the importance of future research. A better understanding of the interaction of propofol with ACTH may be of vital importance in the intra- and post-operative management of patients as well as in diagnostic endocrine testing that involves anasthesia.

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EP1226
A case of IgG4 related hypophysitis in a Caucasian female
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IgG4 related hypophysitis is a recently described entity belonging to the IgG4 related diseases. It is characterised by markedly elevated serum IgG4 levels and tissue infiltration by IgG4 positive plasma cells. To date, 34 cases of IgG4 related hypophysitis have been described but only a handful were in women or biopsy proven. We describe a case of a 58 year old woman who presented with transient headache. She also complained of polypya and nocturia. She had a thyrotoxicoid for treatment of hyperthyroisim 10 years previously. MRI pituitary revealed a pituitary mass with marked diffuse stalk thickening. Dynamic evaluation of her anterior pituitary function revealed raised prolactin and severe GH deficieny. An 8-h water deprivation test showed partial diabetes insipidus. Ferritin, serum ACE, β-HCG, alphafetoprotein, autoimmune screen and ANCA were negative. Chest and abdominal imaging and breast mammography showed no malignancy. A transphenoidal pituitary biopsy showed evidence of hypophysitis with fibrosis and increased number of histologically benign plasma cells and > 10 positive cells per HPF on IgG4 immunocytochemistry, which is highly characteristic of IGG-4 related hypophysitis. Her plasma IgG4 level was normal. She was determined to have IgG4 related hypophysitis as per the criteria proposed by Leporati et al. in 2011. She was commenced on glucocorticoids and is due for a follow up MRI in 6 months. IgG4 related hypophysitis is a rare disorder, which was first described in 2004 based on clinical data. Of the 34 cases recorded in the literature, 29 were men and five were women. The majority of documented cases have been from Japan. While initial case reports were of more severe disease, more recently there have been case reports of patients with milder variants, with one patient reported with normal pituitary function. Accurate diagnosis is essential, as previous reported cases have shown improvement with glucocortiroid therapy. This case illustrates that when an enlarged pituitary gland/stalk is detected, IgG4 hypophysitis should be considered in the differential diagnosis regardless of pituitary function and serum IgG4 level.

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EP1227
Difficulties of acromegaly treatment in young patients: clinical case
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Transphenoidal surgery still appears to be the best option for most of the patients with GH secreting adenomas. In many cases the biochemical cure targets are not reached and the patient needs adjuvant therapy. Alternatives include medical therapy with somatostatin analogues, GH-receptor antagonists and dopamine agonists. These drugs can be used alone or in combination. Radiation therapy with conventional fractionated photons or radiosurgery with proton beam could also be
effective in some cases. We present the clinical case of a 32 year old man, who first came to us in October 2008 due to acral enlargement of hands and feet, proptosis and fatigue. He had a GH level of 52 µg/l and an IGF1 level of 839 ng/ml at the time of diagnosis. After 6 months of therapy with Octreotide (Sandostatin LAR) 20 mg/28 days both of them decreased (IGF1 by 70% and GH by 80%). This treatment was maintained for 2 years, with the persistence of high levels of IGF1 (X 2009-677 ng/ml, VIII- 767 ng/ml), but with the decrease of the tumour and the levels of GH. In August 2011 the patient underwent transsphenoidal surgery (difficult to perform due to severe bleeding and anatomical abnormalities), followed one month later by Gamma Knife. At that point he developed partial pituitary insufficiency (threestot and gonadotropin), hypotension and impaired fasting glucose, for which he started medical treatment. From January 2012 he received again somatostatin analogues (the starting dose was octreotide 20 mg every 28 days for 6 months, followed by 30 mg/28 days) without the normalisation of IGF1 (X 2012-631 ng/ml, V1 2013-403 ng/ml). Because the IGF1 levels were still elevated the dose of octreotide was increased at 40 mg/28 days and GH receptor antagonists (Pegvisomant) was associated (III 2014 10 mg/day s.c.). The following IGF1 levels are still high (Y 2014-493 ng/ml, VII 2014-587 ng/ml, XII 2014-541 ng/ml). The particularity of the case is represented by the age of the patient and by the fact that throughout a relative short period of time he received the latest available therapy in acromegaly.

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**EP1229**

Hyponatraemia in secondary adrenal insufficiency after transsphenoidal surgery for pituitary adenoma: case report

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Introduction

Hyponatraemia is rarely reported as a delayed complication of transsphenoidal resection of pituitary adenoma. Severe hyponatraemia can cause potentially fatal consequences.

Material and methods

A 34 year old patient was admitted as an urgent case at the Clinic of Endocrinology, with symptoms and signs of Addisonian crisis (dizziness, headaches, nausea, vomiting, hypotension), with muscular weakness and muscle aches, tingling hands and confusion. It was a pa-tient diagnosed with acromegaly due to STH secreting macroadenoma, with onset of symptoms 10 days after transsphenoidal pituitary surgery for macroadenoma.

Results

The biochemical analyses showed severe hyponatraemia (Na=116, 118, 122, 136 mmol/l). There were no hormonal dysfunctions de-tected in the pituitary– thyroid and pituitary–gonadal axis, values of STH were 1.6 ng/ml. Because of expressed slow mental process, disorientation and somnolence brain KT was made, showing reduction in the ventricular system, flattened gyri and loss of sulci suggesting cerebral oedema. The con-dition of the patient improved after the correction of hyponatraemia with hydrocortisone therapy.

Conclusion

Postoperative hyponatraemia after transphenoidal surgery is more common than previously reported and may lead to fatal complications. Therefore, all patients should undergo serum electrolyte level monitoring regularly for at least 1 or 2 weeks after transphenoidal surgery.

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**EP1230**

Cushing’s disease in a 7-year-old boy due to corticotroph cell hyperplasia

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Introduction

Cushing’s disease (CD) is very rare in children and is invariably caused by a corticotroph adenoma. However, corticotroph cell hyperplasia has only been convincingly shown in two previous cases of paediatric Cushing’s disease. We report the case of a 7-year-old boy with Cushing’s disease caused by corticotroph cell hyperplasia.

Case report

Our patient presented with a 10-month history of obesity, hirsutism and growth retardation. His height was 2.5 st. below the mean and his weight was over 98th percentile for age. Examination revealed a cushingoid facies, central obesity, striae and hirsutism. Biochemical assessment showed raised 24 h urine free cortisol and mid-night salivary cortisol with failure to suppress serum cortisol following low dose dexamethasone. Baseline 0900 h ACTH level was elevated. A peripheral CRH test showed a brisk rise in ACTH and cortisol consistent with Cushing’s disease. Pituitary MRI was normal. Bilateral inferior petrosal sinus sampling with CRH stimulation showed a central-peripheral gradient >3:1 at 10 min post-CRF confirming the diagnosis of pituitary dependent Cushing’s. The patient underwent endoscopic transsphenoidal pituitary exploration. Abnormal tissue was resected from the left side of the pituitary. Histopathology revealed no adenoma but intense immunostaining for ACTH consistent with corticotroph cell hyperplasia. On the fourth post-operative day, serum cortisol level was 39 mmol/l indicating early remission. Three months post-operatively he remained hypocortisolaemic on hydrocortisone with significant clinical improvement.

Conclusion

This case illustrates that paediatric Cushing’ disease may be caused, albeit very rarely, by corticotroph hyperplasia. Careful follow-up is necessary as the recurrence rate of this entity is not known.

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EP1231
Phaeochromocytoma patient successfully treated after seven myocardial infarctions
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Introduction
Although pheochromocytoma with fatal myocardial infarction has been described over 50 years ago, diagnostics focused on catecholamine secretion is not a routine procedure post myocardial infarction.

Case report
A 49-year-old man, previously healthy, was admitted to the hospital in June 2003, with severe pulmonary oedema. Myocardial infarction was diagnosed on the basis of an increase in markers of myocardial necrosis. There was also found a significant hyperglycaemia and ketoacidosis. Coronary angiography, has not confirmed the changes in the vessels. Due to respiratory failure patient had to be mechanically ventilated. There was even a short-term cardiac arrest. After intensive treatment his status had improved and the patient left the hospital in a stable condition, require two antihypertensive drugs and insulin. In the following years (until 2012) patient has a six NSTEMI. In none of the subsequent coronary angiography important atherosclerotic lesions are visualised. The patient frequent suffered from angina and anxiety. In January 2012 in the left adrenal gland was found in the ultrasound focal lesion, confirmed in tomography as 34 mm high density lesion (50H) with contrast retention. Hormonal diagnostics allowed diagnose adrenal pheochromocytoma. Surgery was delayed for seven and until now the last heart attack (07/05/2012). After the preparation of alpha-blocker, the patient was successfully operated on 05/09/2012. Removal of phaeochromocytoma resulted not only normalisation of blood pressure and the disappearance of the from the coronary symptoms but allowed the metabolic control and improve the patient’s mental state. Currently, the patient is at a good physical and mental condition, treated with a small dose of ramipril, nebivolol and metformin.

Conclusion
The diagnosis of phaeochromocytoma is difficult, although this may change substantially fate of people affected by them. An important clue may be inadequate response to typical treatment.

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EP1232
Primary hyperaldosteronism by Conn’s syndrome: clinical case discussion
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Introduction
Primary hyperaldosteronism (PA) is a disturbance caused by the autonomous production of aldosterone by the adrenal gland. The most frequent causes are due to bilateral supra-renal gland hyperplasia and aldosterone producing adenoma. It is most frequent amongst women aged between 30 and 50 years of age. It is clinically characterised by hypertension (HTN), resistant to therapy. Hypokalaemia, which is known as a ‘classical marker’ is found in less than a third of the patient and is followed by inespecific symptoms (muscle pain/weakness, polydipsy, polyuria, nocturia and parathesia). Diabetes mellitus (DM) can also be found in some cases.

Clinical case
A 55-year-old woman referred from internal medicine due to a adenoma on her right supra-renal gland with hypertension and hypokalaemia. The patient has been hypertensive for the past 16 years with the hypertension being resistant to therapy despite being on four antihypertensives (losartan/hydrochlorothiazide 100 mg/25 mg, carvedilol 25 mg and spironolactone 50 mg). All tests were normal, except a high aldosterone/renin ratio (17.86). The patient was also diagnosed with DM and started on metformin. She was also given KCl for her hypokalaemia. A salt-loading test was carried out that confirmed the diagnosis of HP. (aldosterone 0–35.94; 4 h 56.18 ng/dl). The patient was subjected to a right sided adrenalectomy without complications leading to normokalaemia 48 h after surgery. The aldosterone/renin ratio also normalised. The patient is now able to maintain a normokalaema state and she only needs 10 mg/day of lercanidipine to control her blood pressure.

Discussion
Due to the resistant hypertension before the age of 40 and the lack of experience with or unsatisfactory results obtained by catheterising supra-renal veins the surgical option was chosen in this case. We would like to highlight the importance of monitoring potassium levels on a weekly basis during the first month post surgery due to the risk of transient hipoaldosteronism. With this patient we noticed an improvement in the blood pressure profile during the first month after the surgery. As described in the literature, an improvement or normalisation of hypertension can happen 1–6 months post surgery. However, due to the patient’s long standing hypertension it is unlikely that this will normalise.

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EP1233
Acute renal failure in a patient with hypopituitarism and rhabdomyolysis
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Introduction
Hyponatremia can be a life-threatening emergency. Severe hyponatremia may occur in patients with hypopituitarism and secondary adrenal insufficiency and hypothyroidism. The acute decompensation of pituitary insufficiency can also lead to accompanying rhabdomyolysis and acute renal failure (ARF).

Case report
A 67-year-old woman complaining of general fatigue, dizziness, nausea, feeling cold and numbness of limbs and tongue was admitted to the emergency room. Neurological consultation was made and computer tomography (CT) showed probably old, single, hypodensic ischemic lesion of 6 mm in diameter localized subcortically in the left frontal lobe. Pale skin, loss of axillary hair and scarce pubic hair were found on inspection. The patient’s past medical history was unremarkable and she had not taken drugs permanently. The patient gave birth to three, menopause occurred at the age of 52. Initial laboratory studies have shown severe hyponatremia (Na 116 mmol/l) resistant to the symptomatic treatment. Rhabdomyolysis and acute renal failure developed in the patient. Rhabdomyolysis was diagnosed on the basis of elevated liver enzymes, CK-MB, CPK, and creatinine. The patient was admitted to the Department of Endocrinology. Diagnosis of complete pituitary insufficiency was made on the basis of hormonal profiles. Magnetic resonance imaging (MRI) of the pituitary has shown a very small pituitary gland. Our patient recovered after hydrocortisone and levothyroxine substitution and nephrology treatment. Due to the rhabdomyolysis and ARF the patient required appropriate hydration and a single hemodialysis treatment.

Conclusions
The diagnosis of hypopituitarism in hyponatremic patients can be overlooked and may have grave consequences. Severe hyponatremia and acute renal failure may be the leading symptoms of acute decompensation of pituitary insufficiency. Appropriate hormonal substitution with alert nephrological monitoring and management (including renal replacement therapy if necessary) are crucial in case of acute pituitary decompensation and accompanying complications treatment.

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EP1234

Hemangiopericytoma associated hypoglycaemia and concomitant secondary adrenal insufficiency

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Introduction

Hemangiopericytomas (HPC) are rare vascular tumours that may be associated with hypoglycaemia. Here we report a case of HPC with multiple metastases, accompanying severe recurrent hypoglycaemia due to the combination of different aetiologies.

Case report

A 21-year-old woman was hospitalised due to loss of consciousness. The patient has been diagnosed as HPC by titia mass biopsy 1 year ago. Tumour embolization was made several times. On admission, serum glucose was 42 mg/dl and serum insulin and C-peptide levels were suppressed. GH and cortisol response to hypoglycaemia were found insufficient. Basal ACTH was below 5 pg/mL. IGFBP2 was 25 ng/ml (normal range 116–350 ng/ml) and IGF2 was 823 nmol/ml (normal range 288–736 nmol/ml). The IGF2/IGFBP2 ratio was 3.2 (normal range < 0.1), which indicates unregulated production of IGFBP2. Thorax and abdomen CT imaging demonstrated multiple metastatic lesions in the liver, lung, abdominal cavity, pelvis and bone. MRI revealed a microadenoma in the pituitary gland. In this case, we suggest that hypoglycaemia was associated with the combination of adrenal insufficiency secondary to deficient ACTH secretion, abnormal production of IGFBP2 and diminished hepatic glucose production due to the liver metastases. Because of recurrent severe hypoglycaemic attacks, a continuous glucose infusion was required to maintain normoglycaemia. Prednisolone 40 mg/day was started and a dramatically quick response was observed. Hypoglycaemic attacks were resolved immediately and 20 mg/day prednisolone was needed as maintenance therapy to prevent recurrent hypoglycaemia.

Conclusions

HPC associated hypoglycaemia is a paraneoplastic syndrome usually related with excessive production of IGFBP2 or partially processed forms of pro-IGF2. Hypoglycaemia can also develop by combinations of different factors such as adrenal insufficiency that we observed in the present case. The possibility of other factor must also take into consideration evaluating and treating the hypoglycaemic attacks in patients with mesenchymal tumours.

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EP1235

An unusual case of possible cyclic Cushing’s disease in a young man with Klinefelter syndrome

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Introduction

Cyclic Cushing’s syndrome (CS) is a rare disorder, characterised by alternating periods of normo- and hypercortisolism.

Case report

An 18-year-old young man was followed at the Department of Growth and Reproduction due to Klinefelter and received androgen replacement since the age of 12. As he was shifted to i.m. injections his liver enzymes increased and liver damage due to androgen replacement was suspected. A liver biopsy showed steatosis and, accordingly, androgen replacement was paused. However, the medical history revealed 20 kg weight gain, abdominal striae and mental changes, leading to evaluations for CS. Initial tests showed elevated UFC levels of 213, 238 and 397 nmol/day (ref: 12–150) and borderline abnormal 1 mg dexamethasone suppression test (DST). Over the following months, equivocal test results challenged the clinicians. Repeated long DSTs were normal, UFC levels were fluctuating and, subsequently, a peripheral CRH test showed more than 50% rise in ACTH. Finally, MRI demonstrated a 5 mm hypointense mass in the pituitary gland and an inferior petrosal sinus sampling showed a pituitary-to-peripheral ACTH response > 5, which led to the diagnosis of Cushing’s disease. Two years after first CS suspicion a transsphenoidal adenomectomy was performed. Unfortunately, histology did not reveal signs of an adenoma and during the following years he presented with clinical CS features. He resumed androgen replacement to rule out androgen deficiency as responsible for the symptoms, and liver function tests were unrelated to this. Repeated DSTs showed normal suppression of cortisol despite several elevated UFCs. Thus, the cyclic manifestation of Cushing’s had, very likely, relapsed. The patient had side effects to all possible registered medical therapies for Cushing’s and refuses another neurosurgical procedure.

Conclusions

This case illustrates how overlapping symptoms of cyclic CS and hypogonadism due to lack of androgen replacement further hamper diagnosis and management of cyclic CS.

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EP1236

Accelerated sarcopenia as an initial manifestation of Cushing’s disease

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Introduction

Cushing’s syndrome usually presents with a phenotype including central obesity, striae, hypertension and diabetes. We report a case of Cushing’s syndrome presenting in an atypical way.

Case

A 73 year old lady was referred to neurology with a year’s history of progressive limb wasting, weakness and recurrent falls. The neurology team diagnosed accelerated sarcopenia. Investigations included CK (normal), EMG (suggested myopathic process), nerve conduction studies (no evidence of large fibre neuropathy) and muscle biopsy (atrophy change compatible with on-going neurogenic process). She had a 4-year history of hypertension and type 2 diabetes and morning cortisol was 750 nmol/l. Clinical features included progressive weight loss, immobility, severe muscle wasting and frail skin with extensive bruising and breakdown. Endocrine investigations (18 months post initial presentation) revealed: UFC 1227 nmol/24 h, midnight salivary cortisol 45.1 nmol/l, non-suppressed cortisol following LDDST at 493 nmol/l, normal potassium and ACTH 18 ng/l. Cushing’s syndrome secondary to ectopic ACTH from a malignancy was considered due to the severe clinical features. Initial MRI pituitary was normal. CT whole body showed no evidence of malignancy. Dynamic pituitary MRI revealed area of reduced signal within the pituitary-likely microadenoma. A diagnosis of Cushing’s disease was made and patient was started on metyrapone. On metyrapone 1 g tds her mean cortisol on day curve done by mass spectrometry was 390 nmol/l. Antihypertensives and metformin were discontinued. Concurrent intensive physiotherapy lead to the regaining of limited mobility.

Conclusion

Cushing’s disease can rarely present with severe atypical clinical features that can mimic pathology of various systems, on this occasion accelerated sarcopenia, warranting neurological investigations. It is important to consider and recognise this condition early in order to prevent extreme phenotypes, where regaining full recovery may be prolonged or unattained.

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EP1237

Grossly elevated plasma metanephrine levels due to midodrine, an α1 receptor agonist, in a patient presenting with postural orthostatic tachycardia syndrome

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While phaeochromocytomas are rare tumours, their identification is essential to avoid morbidity and mortality; their biochemical identification is crucial. Plasma and 24 urinary metanephrines are used as first line investigations, with plasma metanephrines increasingly used first due to its simplicity and high sensitivity/ specificity. False positive results, however, can be as high as 20%, particularly secondary to medications; their exclusion is essential to avoid unnecessary imaging and operation. However, most interfering factors cause elevation of less than fourfold above the normal range. In our case, we show the effect of midodrine- an α1 receptor agonist- in causing grossly elevated plasma, but not urinary, metanephrine. 41-year old lady was referred to our endocrine clinic in

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Oxford with a possible phaeochromocytoma. She had 6-year history of dizziness and syncope, initially diagnosed with vasovagal syncope, but latterly diagnosed with postural orthostatic tachycardia syndrome (POTS). Her symptoms were episodic of dizziness, shortness of breath, nausea, headaches, with or without loss of consciousness. Her cardiovascular investigations showed sinus tachycardia and hypotension associated with her symptoms. As part of investigations, plasma metanephrines were assessed and were grossly abnormal: plasma metanephrine > 25 000 pmol/l and normetanephrine of 1758 pmol/l. Her medications included midodrine 7.5 mg 3 b.i.d, bisoprolol and slow sodium. Doxazosin, an α1-adrenoceptor antagonist, had recently been added following the above results. There was no relevant family history, and examination was unremarkable. Investigations included a repeat plasma metanephrines which showed similar results. However, 24-h urinary metanephrines, PTH, thyroid function and pituitary profile were normal, as was adrenal CT scan. Midodrine was then withheld for a week, and plasma metanephrines levels became normal. Doxazosin was subsequently stopped. Most reported drug interference with metanephrine levels cause mild to moderate elevation, due to a variety of mechanisms. We highlight the massive interference in plasma metanephrines assay by the α1-adrenoceptor agonist midodrine.

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EP1240 Pituitary state during conservative treatment of prolactinomas
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Prolactinomas are the most common hormone-secreting pituitary tumors. They have good time of conservative treatment. In the time of diagnostic many pituitary tumors usually can cause hypopituitarism. We have two cases of partially or totally recovery of hypopituitarism in consequence of effective dopamine agonists use. The 24-years man with large prolactinoma (prolactin 52 times higher) and laboratory markers of panhypopituitarism had total recovery in 1 year of cabergoline treatment. The dramatic shrinkage of prolactinoma was observed and the last one was the secondary hypothyroidism which disappeared. The second case is 52 years old man with macroadenoma and ten times higher prolactin. He also has hypogonadism, secondary hypothyroidism and moderate hypocorticotisism (according to laboratory tests). Cabergoline, thyroxine and cortisone were administered. In 1 year despite of tumor shrinkage and prolactin normalisation, testosterone level was still undetected which was qualified as unreversible secondary hypogonadism and testosterone injection were administer. At the same time serum cortisol was at normal-low level and therapy was continued. In one more year the serum cortisol was even more high and the patient reported that he avoided to take cortisone with no consequence as for well-being. He also informed that after several testosterone injection in routine regimen the testosterone level was abnormal high so he discontinued the therapy. After laboratory tests gonadal function was found partially restored with testosterone level slightly lower than lower limit of normal, the level of cortisol was medium-high, but thyroid function remained impaired. Therefore, in case of large prolactin-secreting tumor which leads to hypopituitarism, there is still a chance of at least partially restoring of pituitary function when there is any positive size-dynamic. Our patients didn’t have heavy symptoms of hypopituitarism (except hypogonadism) and was instructed about frequency and expectance from laboratory testing. The thyroid function was the hardest to restore.

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EP1239 A cystic lesion of the adrenal gland mimicking hydatid cyst
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Introduction
Adrenal cystic lesions are uncommon and mostly identified incidentally during radiological investigations or at surgery for unrelated reasons. Its incidence varies between 0.064 and 0.18%. Adrenal cysts are classified as endothelial cysts, pseudocysts, epithelial cysts, and parasitic cysts.

Case report
A 45-year-old female with a past medical history of systemic hypertensive disease for 2 years, presented with recurrent abdominal pain during the last 3 months. Abdominal ultrasonography (US) showed a multicystic mass in the right adrenal region. The CT scan revealed a hypo-dense, multicystic mass measuring 6×5 cm in the right adrenal bed, with slightly mural enhancing after administered with contrast medium and calcifications of the cystic wall. The pictures obtained were very evocative of hydatid cyst. Hydatid serology was negative. An adrenal evaluation was performed and was within normal limits. On the basis of these findings, surgical excision was carried out. The histopathological diagnosis was a cystic PTH-producing tumour in the right adrenal gland.

Conclusion
Cystic adrenal lymphangiomas are very rare, benign vascular lesions. Imaging can characterize the cystic nature of these lesions. However, it sometimes fails to establish a specific diagnosis preoperatively. So definite diagnosis relies on Histologic and immunohistochemical examination. Lymphangiomas must be kept in mind in the clinical and radiologic differential diagnosis of cystic adrenal lesions.

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EP1238 Adrenal crisis due to steroid withdrawal
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Introduction
Corticosteroids are utilised for their anti-inflammatory properties, adreno-cortical atrophy may result. Abrupt steroid withdrawal or intercurrent illness can precipitate acute adrenal crisis. We report two cases of adrenal crisis which resulted from withdrawal of immunosuppressive steroid therapy.

Case report
i) A 74-year-old gentleman was admitted with hypotension (BP 80/40), severe hyponatremia (Na:118 mmol/l) and acute renal failure (Creat 470 mmol/l) and acute kidney injury (CrCl 50 ml/min). The patient was afebrile. He had a history of hypertension and long term immunosuppressive steroid. Laboratory testing showed mild anaemia and white cell count slightly lower than lower limit of normal, the level of cortisol was medium-high (119 mmol/l). BP fell to 102/58 mmHg. An endocrinology consult for hypovolaemia was made and was aware of sick day rules and had no medical alert bracelet. ii) A 76-year-old lady was admitted with hypotension associated with her symptoms. As part of investigations, plasma metanephrines which showed similar results. However, 24-h urinary metanephrines, PTH, thyroid function and pituitary profile were normal, as was adrenal CT scan. Midodrine was then withheld for a week, and plasma metanephrines levels became normal. Doxazosin was subsequently stopped. Most reported drug interference with metanephrine levels cause mild to moderate elevation, due to a variety of mechanisms. Doxazosin was subsequently stopped. Most reported drug interference with metanephrine levels cause mild to moderate elevation, due to a variety of mechanisms. We highlight the massive interference in plasma metanephrines assay by the α1-adrenoceptor agonist midodrine.

DOI: 10.1530/endoabs.37.EPI1238

EP1237 A cystic lesion of the adrenal gland mimicking hydatid cyst
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Introduction
Adrenal cystic lesions are uncommon and mostly identified incidentally during radiological investigations or at surgery for unrelated reasons. Its incidence varies between 0.064 and 0.18%. Adrenal cysts are classified as endothelial cysts, pseudocysts, epithelial cysts, and parasitic cysts.

Case report
A 45-year-old female with a past medical history of systemic hypertensive disease for 2 years, presented with recurrent abdominal pain during the last 3 months. Abdominal ultrasonography (US) showed a multicystic mass in the right adrenal region. The CT scan revealed a hypo-dense, multicystic mass measuring 6×5 cm in the right adrenal bed, with slightly mural enhancing after administered with contrast medium and calcifications of the cystic wall. The pictures obtained were very evocative of hydatid cyst. Hydatid serology was negative. An adrenal evaluation was performed and was within normal limits. On the basis of these findings, surgical excision was carried out. The histopathological diagnosis was a cystic PTH-producing tumour in the right adrenal gland.

Conclusion
Cystic adrenal lymphangiomas are very rare, benign vascular lesions. Imaging can characterize the cystic nature of these lesions. However, it sometimes fails to establish a specific diagnosis preoperatively. So definite diagnosis relies on Histologic and immunohistochemical examination. Lymphangiomas must be kept in mind in the clinical and radiologic differential diagnosis of cystic adrenal lesions.

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EP1241 Pituitary apoplexy in Cushing’s disease after a standard low-dose dexamethasone suppression test
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Introduction
Pituitary apoplexy is caused by an infarction or a haemorrhage in a pituitary adenoma manifesting in acute headaches, consciousness impairment, endocrine features, and moderate to severe visual loss, with chiasmal syndrome or ocular motor palsies.
Case report
We describe here a case of a 25 years old woman, followed in our institute for a Cushing disease, and who underwent a pituitary apoplexy 24 h after a standard low-dose dexamethasone suppression test. In fact our patient presented a clinical outcome of a intra cranial hypertension, made of headache, vomiting associated to a loss of visual field and oculomotor palsies. MRI demonstrated classical signs of apoplexia. Patient was treated by cortico-therapy for one week with no response, leading to a surgical management. After what we could rapidly appreciate an improvement in the visual symptoms.

Conclusion
The clinical picture of pituitary apoplexy is characterized by the sudden onset of oculomotor palsy or blindness with acute headaches and even consciousness impairment. A functional and vital risk is present because of acute hypopituitarism. This emergency diagnosis is confirmed by tomodensitometry or magnetic resonance imaging. The association of hormone substitution and tumour transphenoidal resection commonly leads to a positive outcome and visual improvement.

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EP1242
Hypopituitarism after miscarriage: a case report
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Introduction
Sheehan’s syndrome (SS) is a cause of partial or total hypopituitarism that occurs after postpartum pituitary infarction, in the context of severe bleeding and/or hypotension. With the advancement of obstetric care, it has become a rare disease in developed countries, but its prevalence may be underestimated. Clinical presentation is dependent on the severity of hormonal deficits, is often nonspecific and many women may be asymptomatic for years. These reasons contribute to a delay in diagnosis and in treatment of a significant cause of morbidity and mortality in affected women.

Clinical case
We report a case of a 32 years old woman sent to endocrinology consultation because of hypogonadotrophic hypogonadism. Past history: menarche at 11 years with regular cycles, two pregnancies, a normal delivery without complications (17 years) and a miscarriage at 8 weeks gestation (28 years). After the miscarriage, she was hospitalised with anaemia and needed blood transfusions. She’s amenorrhoeic since the miscarriage. Currently, she’s asymptomatic and desires another pregnancy. On physical examination, highlight for a low BMI (17 kg/m²). Analytically, FSH 1.08 mIU/ml (2.5–10.2), LH <0.07 mIU/ml (1.9–12.5), oestradiol 63.89 pmol/l (71.6–529.2), TSH 1.43 µU/ml (0.358–3.74), T4 0.75 ng/dl (0.76–1.46), prolactin 4.67 ng/ml (2.8–29.2), cortisol 13.6 µg/dl (4.3–22.4), ACTH 19.7 pg/ml (<46), somatotelin 110 ng/ml (115–307), testosterone <10 ng/dl (<14–76), normal DHEAS and androstenedione. Insulin induced hypoglycaemia reveals normal response of cortisol and GH. Pituitary MRI revealed a concave gland with lower dimensions than expected for her age. She was treated with levothyroxine 50 µg/day and oriented to assisted reproductive consultation.

Discussion
The patient presented corresponds to a case of hypopituitarism due to probable pituitary infarction after abortion. We emphasise the importance of the evaluation of pituitary function in women with childbirth history associated with significant blood loss, even several years after the episode.

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EP1243
Acromegaly caused by atypical pituitary adenoma
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Introduction
Atypical pituitary adenomas have higher risk of aggressive behaviour in particular by the higher growth, local invasion and high risk of recurrence after surgery. In acromegaly the resistance to somatostatin analogues may be another manifestation of these adenomas since higher levels of Ki-67 are associated with poor response to therapy.

Case report
A 41-year-old woman presented to our consult with history of headaches, growth of the hands, hyperhidrosis, carpet tunnel syndrome and enlargement of the lips with 3 years of evolution. She also mentioned complaints of neck pain and reported an episode of visual changes that reversed spontaneously. Hormonal evaluation revealed the following alterations: IGFI 1687 µg/dl (64–336), GT basal 25.6 ng/ml (<8) and a lack of GH suppression to <1 ng/ml on oral glucose tolerance test. Pituitary MRI revealed pituitary lesion with 24 mm craniocaudal diameter and 5 mm transverse diameter with invasion of the cavernous sinuses. She was submitted to transphenoidal resection. Tumour pathology showed diffuse expression of GH, prolactin multifocal expression and absence of expression of other pituitary hormones. Ki-67 labelling index was 8%. Sparse representation of p53.

Conclusion
Atypical pituitary adenoma. The MRI repeated 3 months after surgery showed persistence of tissue attributable to residual tumour invading the right cavernous sinus. The patient began treatment with somatomatostatin analogues. This is a case of acromegaly with several predictors of a possible failure of response to somatostatin analogues: young age, elevated levels of GH and IGFI at diagnosis, macroadennoma with invasive growth and Ki-67 labelling index of 8%. In the presence of cases of atypical adenomas a multidisciplinary team of endocrinologists, neurosurgeons, pathologists and oncologists must work together in attentive and personalised follow-up of the patient in order to prevent disease progression.

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EP1244
Slipped upper femoral epiphysis: a rare clinical manifestation of MEN2: a case report
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Introduction
Multiple endocrine neoplasia type 2 (MEN2) comprise a group of heritable disorders that result from mutations in the RET proto-oncogene on chromosome 10. MEN2 is sub classified into MEN2A and MEN2B; these syndromes are characterised by the development of tumours at multiple sites. MEN2A is characterised by medullary thyroid cancer, pheochromocytoma, and primary parathyroid hyperplasia.

Description/case presentation
The index case is a 49 year old female with a recent diagnosis of right pheochromocytoma on screening for known MEN2A. Her mother had a parathyroidectomy, a partial thyroidectomy and bilateral pheochromocytoma. The index case had a total thyroidectomy in 1980 at which time C cell hyperplasia was noted. Diagnosis was confirmed by RET oncogene mutation analysis. She has three children who are MEN2A positive and are undergoing screening. Her daughter was diagnosed with a pheochromocytoma in 2006 with a subsequent unilateral adrenalectomy. There is also a family history of slipped upper femoral epiphysis; she had an unilateral SUFE in her teens prior to her diagnosis of MEN2A. Her daughter underwent surgery for bilateral SUFE at the age of 11 and 12. SUFE is the most common hip disorder affecting the adolescent population; there are believed to be multiple aetiological factors. In the literature, SUFE has been attributed to endocrine pathologies including hypergonadism and panhypopituitarism, deranged parathyroid hormone function and hypothryoidism. Both the index case and daughter were slim and had no history of trauma therefore atypical for SUFE.

Discussion/conclusion
We postulate that changes in parathyroid hormone or fluctuations in T4 level in response to replacement during adolescence may have contributed to the development of SUFE in this family. Patients with MEN2A may be particularly vulnerable to this disorder because of their young age at the time of endocrine disturbance. This has not been reported previously in the literature.

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EP1245
Simultaneous diagnosis of Graves’ hyperthyroidism and adrenal insufficiency
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Introduction
Patients with autoimmune diseases are known to develop other autoimmune conditions. Adrenal insufficiency of autoimmune etiology is known to coexist with autoimmune diabetes mellitus, Hashimoto’s thyroiditis and vitiligo. However, Graves’ disease in the context of adrenal insufficiency is rare.

Aim
The aim was to describe the case of a patient who presented with fatigue and was diagnosed to have hyperthyroidism and adrenal insufficiency of autoimmune etiology.

Case report
A 30-year-old male patient was evaluated by his family physician because of fatigue, tachycardia and weight loss. He was found to have high free T4 levels and TSH 0.001 mIU/l. Antithyroid drugs were administered. However, the patient complained of continuing fatigue and weight loss. He had dark colored skin. However, when his photos were compared to older ones it appeared that his skin had a darker color. Morning cortisol and ACTH were measured. Cortisol was found to be very low and ACTH high. Cortisol was administered along with antithyroid medications and the patient improved. TSH receptor antibodies were positive and anti-adrenal antibodies were also positive. On clinical examination as well as ultrasoundography the patient had no evidence of Graves’ ophthalmopathy.

Conclusions
Autoimmune diseases may coexist with other autoimmune conditions, which usually develop sequentially. However, even in young patients, the simultaneous development of more than one endocrine autoimmune conditions cannot be excluded, and it should be included in the differential diagnosis, especially if symptoms persist.

EP1246
Fatigue as the presenting symptom of multiple endocrine neoplasia of type 2A
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Clinical spectrum of phaeochromocytoma syndromes are very heterogeneous. Sometimes life threatening hypertensive attacks may be the presenting symptom or the clinical picture may be subtle that a nonspecific symptom like fatigue can lead to diagnosis. We herein present two phaeochromocytoma cases with distinct clinical features.

Case 1
A 20-year-old female patient admitted to emergency department with blurred vision and headache. She experienced headache for 3 years and once she had a seizure and lost consciousness for 4 h. During the coarse blurred vision recurred and examination revealed papilledema and retinal haemorrhage. Thorax CT-angiography performed for a presumptive diagnosis of Takayasu’s arteritis revealed a 3.5-cm right adrenal mass, and she was referred to our endocrinology clinic. She was hypertensive, and urinary catecholamines were very high. She had no family history of phaeochromocytoma and work-up for hereditary syndromes were negative. After preoperative preparation, she was successfully operated. Histopathological examination was compatible with phaeochromocytoma.

Case 2
A 30-year-old male patient was evaluated by his family physician because of fatigue. He was anxious as his father died of metastatic brain cancer. His urinary and plasma catecholamines were very high. He underwent bilateral adrenalctomy, and pathologic examination confirmed phaeochromocytoma. RET protooncogen was positive, and total thyroidectomy revealed multifocal medullary thyroid cancer.

Conclusion
Fatigue can be the presenting symptom of MEN2A, and clinical picture does not correlate with the extent of disease in phaeochromocytoma syndromes.

EP1247
Ectopic ACTH syndrome due to a pancreatic neuroendocrine tumour: a case report
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The ectopic secretion of corticotropin from no pituitary tumours causes ~10–20% of cases of Cushing’s syndrome. Enteropancreatic neuroendocrine carcinoma represents a rare cause of ectopic ACTH syndrome.

Case
A 51 years-old woman without past medical history was admitted by gain weight, facial oedema 4 months previous. Physical examination: BP 167/124, cardiac rate 49 bpm, facial oedema, truncular obesity. No others abnormalities. Laboratory test. Glucose 148 mg/dl. Kaliemia 2.8 mEq/l. Cortisol 102 µg/dl, FCU 4000 µg/24 h. chromogranin A 526 ng/ml, indocalcic acid 6.8 mg/24 h. Nocturnal cortisol 132 µg/dl. ACTH: 427 µg/ml. Nagment test. Cortisol 129 µg/dl. Suppression with 8 mg of dexamethasone: cortisol basal 141 µg/dl, post 146 µg/dl. ACTH basal 577 pg/ml post 586 pg/ml. CT scan revealed a pancreatic mass of 30x20 mm and enlargement of adrenal glands. PET scan displayed abnormal accumulations of fluorodeoxyglucose in pancreatic area, distribution at multiple sites in the liver and enlargement of both adrenal glands. Surgical procedure was carry out, and large pancreatic tumour with multiples hepatic metastasis were observed. Pancreatectomy and splenectomy was carry out. Hystopatological study showed pancreatic neuroendocrine tumour, positive to chromogranin, sinapofisine and CKAEL1-EI3, Ki 67 up 50%, with lymph nodes and liver metastasis of neuroendocrine tumour. Surgical treatment of adrenal gland was discarded. Treatment with ketoconazole and metyrapone was initiated without improvement and mifepristone was added, lowering cortisol levels, however, outcome was unfavourable and patient died 3 months after diagnosis by respiratory distress and complications of Cushing’s syndrome.

Discussion
Patients with pancreatic neuroendocrine carcinoma represent a rare cause of ectopic ACTH syndrome. A typical Cushingoid appearance is less frequent in ectopic ACTH syndrome. Treatment of ectopic ACTH syndrome is excision of the primary tumour. However, curative surgery is successful in only 30–47%. If the tumour cannot be resected, bilateral adrenalectomy offers effective permanent treatment. Medical cortisol inhibitors include ketoconazole, metyrapone.

EP1248
Bullous pemphigoid induced by vildagliptin
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Introduction
Bullous pemphigoid (BP) is an uncommon chronic, autoimmune, and subepidermal disease. It can be associated with drugs, u.v. irradiation, and X-ray therapy. There is a number of reports on bullous pemphigoid (BP) induced by DPP-IV inhibitors (vildagliptin, sitagliptin, saxagliptin). The enzyme DPP-IV degrades glucagon like peptide 1 (GLP-1), which is a potent stimulator of insulin production (release and secretion. DPP-IV (CD26), present as a cell surface molecule on immune cells, also plays an important costimulatory role in immune activation. We present a case of BP induced by vildagliptin.

Case report
A 56-year-old male patient who was diagnosed type 2 DM had initial Hba1c level of 12.90%. Initial therapy with premix biphasic aspart insulin bid was switched to metformin and vildagliptin 50/1000 mg combo pill bid after A1c level dropped to 5.7% at 9 months of insulin therapy. Five months after vildagliptin was started, tense vesicles 8–10 in number with an erythematous base developed over forearms and cruris. Histologic examination of lesions yielded BP. Oral antibiotics was discontinued. He was followed up with diet alone. He did not
adhere to the therapy of oral flutamid and azathioprine and topical steroid. But the lesions regressed spontaneously after cessation of antidiabetics. Clohsetosol propionate cream bid was continued. A1c was 5.7% 5 months after discontinuation of viluglipentin and metformin.

Conclusions
In the literature onset of BP lesions took 10 days to 2 years. Mostly the patients were on combo therapy with metformin. The lesions improved dramatically after cessation DPP-IV inhibitors avoiding necessity for systemic treatment for BP. Elder males predominate. This is the first case of BP induced by DPP-IV inhibitors in Turkey.

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EP1249
Adjustment disorder and hypertensive episodes associated with cross-sex treatment with testosterone
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Introduction
Testosterone treatment in female-to-male transsexuals has been associated with worsened cardiovascular risk factors, acne, male-pattern baldness and more rarely with the onset of hypertension. Another frequent side effect of the treatment is aggression proneness - but rarely actual aggression- and increased libido.

Case report
We present the case of a 17-year old transsexual patient referred for initiation of testosterone treatment. A low initial dose (20 mg daily as a topical gel) elicited acne and mild transient mood changes (increased libido, occasional aggressive ideation) without blood pressure elevation. These symptoms improved after the first month. Three months later, after increasing the dose to 40 mg, the patient presented boats of anger, aggression proneness, and coincidentally headache and hypertensive episodes. Secondary hypertension was ruled out and an ambulatory blood pressure monitoring showed blood pressure peaks up to 192/113 mmHg, with tachycardia up to 123 bpm and a mean activity blood pressure of 138/87 mm Hg. The patient was diagnosed of adjustment disorder, received short-course psychotherapy and testosterone was withdrawn. After one month, the mood disorder had abated, without new episodes of headache and hypertension. A second ambulatory blood pressure monitoring showed no hypertensive peaks with a mean activity blood pressure of 124/71 mmHg. According to the patient’s wishes, low-dose testosterone treatment was reinstated with a scheduled slow dose progression; So far, the patient remains asymptomatic and normotensive.

Conclusions
Our patient suffered hypertensive episodes in the context of an adjustment disorder associated with testosterone treatment. Withdrawing testosterone resolved both the adjustment disorder and the hypertensive episodes. We consider that the increased blood pressure was not a direct consequence of testosterone, but an indirect result mediated by untoward psychological reactions of the patient.

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EP1250
Submandibular ectopic thyroid with normally located thyroid gland
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Ectopic thyroid is a rare developmental anomaly of the thyroid gland which is defined as the presence of thyroid tissue at a site other than the pretracheal area. Nearly 1–3% of all ectopic thyroids are located in the lateral neck. Simultaneous submandibular ectopic thyroid tissue presenting with a functional orthotopic thyroid gland is extremely rare. A 37-year-old woman was admitted to our outpatient clinic with a cervical mass existing for 3 years. On physical examination, a painless, uniformly bounded, mobile, soft, nearly 3x4 cm mass was observed in the right submandibular region. A detailed systemic examination did not reveal any abnormality. Ultrasonography of the neck demonstrated a solid mass of 34x36x26 mm, including cystic areas and showing significant blood flow, localized in the right submandibular region. Her thyroid gland was in a normal location and had normal parenchyma. Thyroid tests confirmed euthyroidism and she had no anti-thyroperoxidase or antithyroglobulin antibodies. Ultrasonographically guided fine needle aspiration biopsy was non-diagnostic. Cervical magnetic resonance imaging revealed a 35x41x26 mm lobulated mass showing contrast agent involvement in the right submandibular region and a normal orthotopic thyroid gland. The patient underwent excision of the submandibular mass under general anaesthesia. The histopathological examination of the mass revealed thyroid gland tissue with nodular hyperplasia. She was symptom free and euthyroid over the next year and there was no evidence of recurrence. Ectopic submandibular thyroid tissue is an extremely rare event that poses both diagnostic and management problems. However, physicians should be aware of the possibility that a submandibular mass could be ectopic thyroid tissue.

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EP1252
Euthyroid Graves’ ophthalmopathy in a patient with long-term amiodarone treatment
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Introduction
Ophthalmopathy, the most common extrathyroidal manifestation of Graves’ disease, occurs in 5% of cases in the absence of hyperthyroidism. Amiodarone, an iodine-rich antarrhythmic drug, causes thyrotoxicosis or hypothyroidism, but its effect on thyroid autoimmunity is still a matter of debate.

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Case report
We report the case of a 58-year-old woman, suffering from non-sustained ventricular tachycardia, treated incorrectly with amiodarone for 27 years. Thyroid function was normal until January 2014 when she developed amiodarone induced hypothyroidism (TSH = 24 mUI/ml with negative thyroid autoantibodies anti-Tg=0.1 UI/ml (<4), anti-TPO = 1.0 UI/ml (<20), and substitutive therapy with l-thyroxine 50 μg/day was started. Three months later the patient stopped l-thyroxine at an L-thyroxine level of 1.6 mUI/ml. Subsequent evaluation in August showed a normal thyroid function (TSH = 3.4 mUI/ml). In October she was referred to our Department for periorbital oedema, increased tearing, diplopia, mild conjunctival injection. The laboratory tests showed euthyroidism (TSH = 5.88 mUI/ml, negative anti-Tg and anti-TPO antibodies, positive TRAb=6.8 UI/l (<1). Thyroid ultrasound was normal. The eye examination revealed a clinical activity score of 4, decreased left eye motility, vertical diplopia and Hertel exophthalmometer measurements were 15 mm on the right and 17.5 mm on the left eye. The orbital CT-scan showed thickening of the left eye inferior and medial rectus muscle. The patient was treated with six pulses of intravenous methylprednisolone, 250 mg once a week, but after the third pulse she developed symptomatic bradycardia. The cardiologist recommended to stop amiodarone. The remaining pulses were well tolerated, with improvement of the eye symptoms.

Conclusion
In our case this variable thyroid status and the occurrence of euthyroid Graves’ ophthalmopathy (GO) sustain the finding that in susceptible individuals amiodarone may precipitate thyroid autoimmunity due to its cytotoxic effect with a greater release of thyroid antigens. Patients with euthyroid GO need regular follow-up, because the eye involvement may develop before the appearance of clinical or laboratory signs of hyperthyroidism.

EP1253
Squamous cell thyroid carcinoma, the importance of early diagnosis and treatment
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Introduction
Squamous cell thyroid carcinoma is a very rare malignant epithelial tumour. It presents as rapid growth cervical mass, may affect neighbour structures and sometimes metastasizes other parts of the body. It’s often associated with previous goiter history and occasionally with autoimmune thyroiditis. It can appear pure, as a component of undifferentiated carcinoma, or combined with differentiated carcinoma areas (papillary or follicular).

Case report
A 31 years old woman, with goiter family history (mother and paternal aunt). Without any previous history or cervical radiotherapy. She presented with asymmetric left anterior cervical lump, without compressive discomfort. Physical examination: multinodular goitre (MNG) grade 2. Neck ultrasound: bilateral MNG with endohoracic projection and left prevalence with 3 cm dominant nodule. Biochemistry: TSH 1 μU/ml. Ultrasound-guided FNA: colloid nodule with cyst formation. X-ray chest: left-extrinsic tracheal mark. Because of nodules size and endohoracic projection, we decided total thyroidectomy. Histopathology: colloid nodules with peripheral areas of squamous metaplasia, including nuclear atypia, mitosis and p53 expression suggestive of squamous carcinoma transformation, the tumour doesn’t exceed the capsule, there were no lymphatic or vascular infiltration. Extension post-surgery, we apply for a thyroid ultrasound with suggestive image of scar tissue in left thyroid bed and PET-CT was negative. Oncology Service examined our case, no adjuvant treatment was recommended. Currently, three years after surgery, the patient remains free of disease.

Conclusion
Squamous cell thyroid carcinoma is an aggressive tumour, usually lethal. It requires rapid diagnosis. The best option of treatment is radical surgery, only possible if early diagnosis, as in our case. The use of postoperative external radiotherapy or adjuvant chemotherapy should be considered because of the high rate of local recurrence of these tumours.

EP1254
A rare case of triple parathyroid adenoma with hyperparathyroidism occurring at a young age
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Lesions causing primary hyperparathyroidism (PHP) can be summarised as solitary adenoma (80-85%), multinodular hyperplasia (15%), parathyroid carcinoma (1%). While double adenomas are identified in 2–15% of the patients which are operated for PHP, triple adenomas are very rare. The case is presented because in the recent years patients who are admitted to the hospital with intense bone complaints are very unusual and multiple adenomas are also seldom. 22 years old female patient was admitted to orthopaedics outpatient clinic with symptoms of severe pain with activity and mass at proximal area of left femur. During evaluation calcium and parathyroid hormone (PTH) levels were discovered to be high. Calcium: 11.8 mg/dl, phosphorus: 2.2 mg/dl, alkaline phosphatase (ALP): 1275 U/l, PTH: 2754 pg/ml, 24 h urine calcium: 288 mg/day, BUN: 5 mg/dl, creatinine: 0.41 mg/dl, 25 (OH) D Vitamin: 3.2 μg/l. Thyroid doppler ultrasonography revealed a 20×17×7 mm mass at the right lobe of the thyroid and at the caudal region of this lesion a 13×11×9 mm mass, also a 36×22×23 mm lesion at the left lobe of the thyroid continuing to the mediastium consistent with right and left-sided parathyroid adenomas. 20 mCi Tc-99m MIBI SPECT images demonstrated hyperdense activity only at the left side. Before the operation the patient was screened for multiple endocrine neoplasia because of her young age, results were negative. After the operation three parathyroid adenomas were discovered and PTH and calcium levels regressed to 10 pg/ml and 8.4 mg/dl respectively. Usually PHP is expected to occur at later stages of life, but PHP should also be kept in mind in patients with serious bone complaints, high calcium and PTH levels. Early diagnosis and appropriate treatment can prevent morbidity and mortality related with PHP.

EP1255
A case of Gitelman syndrome with normomagnesemia: do detailed history and basic laboratory tests provide correct diagnosis?
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Introduction
Gitelman syndrome (GS) is autosomal recessive disorder, characterised by hypokalemia, hypomagnesemia, metabolic alkalosis and low urinary calcium excretion. We report a case with final diagnosis of GS using the DNA analysis, presented with severe hypokalemia but normomagnesemia.

Case report
A 47-year-old Japanese male presented to our hospital because of severe hypokalemia in the annual health check-up. Severe hypokalemia was pointed out in the previous check-up, but he was reluctant to be investigated. He was totally asymptomatic and had no history of muscle weakness, palpitation and syncpe. He denied the use of any medication including laxative and diuretics. He was normotensive and no growth retardation. The laboratory test revealed that the serum potassium was 1.7 mEq/l but he had no hypomagnesemia. His 24 h-urinary calcium excretion, 75 mg/day, was not so impaired. We analysed his genetic mutation by direct DNA sequencing. As a result, he had two genetic mutations on SLC12A3 which encoded the thiazide-sensitive NaCl cotransporter. These genetic mutation are found in the majority of GS patients. We established a final diagnosis of GS based on his history and genetic mutations.

Discussion and conclusion
To make a diagnosis of GS, many aetologies should be excluded. Especially, Bartter syndrome is an important genetic disorder to distinguish. Especially, type III Bartter syndrome has similar features with GS, adult-onset, no growth retardation, preserved renal function and similar electrolyte abnormalities. To evaluate serum magnesium and urinary calcium excretion were important for the differential diagnosis. In this case, the serum magnesium was normal and urinary calcium excretion was not decreased. This case didn’t have classical features.
of GS. To identify the genetic mutation is very important to establish a diagnosis of GS. When the laboratory findings are not typical for GS, direct DNA sequencing can be useful test to distinguish with Bartert syndrome.

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EP1256
Clinical features and surgical approach of thyroid pathology in patients over 65 years
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Introduction
The significant increase in the average lifespan of the general population lead to a proportional enhancement in the prevalence of benign and malignant thyroid conditions and equally the number of surgeries for this pathology.

Patients and method
In a personal series of 464 thyroid disorders undergoing surgery over two decades we recorded 51 patients (21.5%) aged over 65 years of which 11 (2.4%) having over 75 years. Demographic, clinical and diagnostic characteristics of these cases were together with indications, management practice and outcome.

Results
There have been recorded 33 females and 18 males (R = 1/1) with clinically, laboratory and histologically confirmed diagnosis in which were 22 (multi) nodular goitres (47%) among 16 six plunging goitres some with compressive phenomena, 18 (35.2%) – two Basedow diseases, nine multinodular toxic goitres and seven toxic adenomas and also nine thyroid carcinomas (17.6%) of which six were differentiated and three anaplastic tumours. Thirty-four total or near-total thyroidecstomies in which three with cervical lymphadectomy and l7 conservative exercises were performed. There were not postoperative deaths but we recorded two cases each of prolonged hypocalcaemias, recurrent laryngeal nerve paresis and one recurrence. In all benign cases we obtained a stable in time cure while in obtained in four papillary tumours.

Discussions
Our series as well as literature data emphasises out of increased prevalence of thyroid geriatric disorders underling peculiarities related of sometimes delayed occurrence and prolonged evolution, atypical or imprecise symptomatology with less conclusive bioassays, coexistence of burdensome comorbidity all of them with direct consequences of a possible surgical sanction. In terms of clinical and lesional aspects outside thyroid nodules and especially micro-nodules that can accommodate any substrate, hyperthyroidism are much more (multi)nodular and they have mostly atypical manifestations, ophthalmopathy and hyperkinetic syndrome being sometimes replaced by an ‘apathetic’ presentation with weight loss and predominantly cardiovascular syndrome j arrhythmia and cardiac failure.

Finally thyroid carcinomas have increased aggressiveness, accelerated evolution, higher incidence of anaplastic forms. Principles of thyroid surgery in the elderly are the same with those adopted at younger ages also taking into account the pathological load of the subjects and its mandatory preoperative correction.

Conclusions
Despite some difficulties in diagnostic and additional risks related to comorbidity benign and malignant pathology installed in patients over 65 years, may benefit of all types of conservative or radical thyroidectomies in terms of strict monitoring individualised in each case.

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EP1257
Incidental papilar carcinoma and large goitre in extremely obese patient with excessive daytime sleepiness
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Introduction
In adults, the most common cause of obstructive sleep apnoea is obesity. Other causes are anatomical craniofacial bony abnormalities, neurologic syndromes, alcohol and sedatives use, hypothryosim, acromegaly and rarely thyroid goitre. Untreated obstructive sleep apnoea can lead to serious complications, including cardiovascular diseases, accidents, and premature death.

Case report
A 56-year-old patient was referred to a pulmolologist due to excessive daytime sleepiness. Patient has primary hyperthyroidism adequately treated with a constant daily dose of levothyroxine (L-T4). The scores for the Epworth sleepiness scale was 15. The severe obstructive sleep apnoea (OSA) was confirmed by polysomnography (Respiromics Alice 5): apnoea-hypopnmia index (AHI) was 32.6/h. Spirometry showed a restrictive pattern related to obesity. Due to primary hypothyroidism and obesity examination by an endocrinologist was advised. Patient was extremely obese - BMI 45.3 kg/m2 with neck of 50 cm in circumstance and large goitre. Ultrasonography of the neck revealed a large goitre with significant retrosternal propagation and some thyroid nodules. Volume of the right lobe was 120 ml whereas the volume of the left one was 92 ml with a tracheal compression. Due to large goitre a total thyroidectomy was conducted. Pathohistology report was showed chronic lymphocytic thyroiditis and papilar carcinoma with diameter of 1.8 cm in the left lobe. The patient postoperatively received therapeutic dose (3.7 GBq) of Iiodine I. There were no significant changes of the patient’s weight. Six months after the surgery polysomnography was repeated.

Conclusion
Thyroid cancer coincided with large goitre which was an additional cause together with extreme obesity for OSA. In obese patients with excessive daytime sleepiness, additional endocrine causes of OSA should be considered.

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EP1258
A rare case of syndrome of inappropriate antidiuretic hormone
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Introduction
Acute intermittent porphyria (AIP) is an autosomal dominant disorder resulting from partial deficiency of the haeme biosynthetic enzyme porphobilinogen deaminase.

Case report
A 17-year-old female presented with progressive abdominal pain. She had history of recurrent abdominal pain and darkening in urine colour. She was on lansoprazol and metaclopamide, initiated 2 days earlier. She did not have additional personal or relevant family history. Physical examination did not reveal any pathologic finding.

Laboratory findings were as following: glucose: 84 mg/dl (N: 74–106), urea: 14 mg/dl (N: 17–43), creatinin: 0.6 mg/dl (N: 0.5–0.9), sodium: 33 mmol/l (N: 136–146), potassium: 3.6 mmol/l (N: 3.55–1), chloride: 76 mmol/l (N:101109), ALT: 21 U/l (N: 0.35), CK: 281 U/l (N: 0.145), triglyceride: 46 mg/dl (N: 0–150), total protein: 6.9 g/dl (N: 6.6–8.3). In urine sediment erythrocyte was 17 p/Hpf (N: 0–2), leucocyte was 60 p/Hpf (N: 0–2), and nitrite was (+). Search for euvolemic hyponatraemia was initiated. Sodium in spot urine was 95 mmol/l, urine osmolality was 490 mosm/kg and plasma osmolality was 230 mosm/kg. TSH was 3.1 IU/ml (N: 0.3–5.6) and basal morning cortisol level was 34 mg/dl (N: 6.7–22.6). She was diagnosed with syndrome of inappropriate ADH, Plasma Na level was gradually increased up to 133 mmol/l with infusion of %0.3 NaCl solution. Chest X ray, cranial MRI and abdominal ultrasonography did not reveal any abnormality. Based on her history of periodic abdominal pain and dark urine porphyria was suspected. Porphobilinogen in 24-h urine sample was 19.7 mg/24 h (N: 0–18). Total porphobiligen in 24-h urine sample was 19.7 mg/24 h (N: 0–18). Total porphyrin was 646 g/24 h (N: 0–100). She did not have any cutaneous lesions. With the laboratory findings and her personal history she was diagnosed with inappropriate ADH syndrome secondary to AIP. The acute attack of AIP was taken under control with glucose loading and antiobiotherapy for urinary tract infection.

Conclusion
It is important not only to treat syndrome of inappropriate ADH, but also to address any underlying condition. Diagnosis and management of AIP can be challenging and close monitoring for complications is needed.

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EP1259

Fine needle aspiration biopsy: a method to distinguish between thyroid nodules and parathyroid adenomas
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Introduction
High-resolution ultrasound (US) allows the location of large parathyroid adenomas. These tumours should be however differentiated from thyroid nodules. For the confirmation of the parathyroid adenoma, we propose US-guided fine-needle aspiration biopsy (FNAB) of suspected nodules, with additional parathyroid hormone (PTH) analysis in the washout of the aspirate (PTH-FNA).

Case report
A 51-year-old woman with recently installed menopause and a history of kidney lithiasis and fragility fractures attended our hospital for the investigation of a multinodular goitre. The measurement of bone mineral density assessed by dual X ray absorptiometry showed that the patient was severely osteoporotic, with lowest score on distal 1/3rd of the radius. Despite the presence of complications, the high PTH level (281 pg/ml) was accompanied by only marginally increased serum calcium (10.1 mg/dl). This discrepancy may be explained by the co-existence of D hypovitaminosis (11 ng/ml). Ultrasound investigation revealed the presence of a multinodular goitre containing five nodules, one of them showing features suggestive for a large parathyroid adenoma. We measured high PTH levels only in the FNAB washout from the suspected parathyroid adenoma, but not in that extracted from the largest of the other thyroid nodules. The patient was submitted to total thyroidectomy due to compressive complaints and excision of the parathyroid adenoma. Immediately after surgical intervention, the PTH levels normalised. Histology confirmed pre-surgical localization of the parathyroid adenoma and revealed that one of the thyroid nodules contained an in situ papillary carcinoma.

Conclusion
PTH-FNA is a reliable and possibly a more accurate and faster method than additional imaging techniques to localise a large parathyroid adenoma in patients with concomitant thyroid nodules.

Disclosure
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EP1260

Hypercoagulable state: an evidence of linkage with hyperthyroidism
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Introduction
Hyperthyroidism is not a widely recognised association with Venous thromboembolism (VTE). However, several previous studies suggest that hyperthyroidism represent a potential hypercoagulable and hypofibrinolitic state, which may contribute to the increased risk of thromboembolism.

Case report
A 39-year-old lady presented with Swelling over bilateral lower limbs for 1 month, Palpitation for 1 month. She had history of swelling over neck for last 13 years and protrusion of bilateral eye for 13 years, history of increased 1 month, Palpitation for 1 month. She had history of swelling over neck for last 13 years and protrusion of bilateral eye for 13 years, history of increased

Conclusion
Our case report reinforces the available evidence on the possible role of overt hyperthyroidism as VTE risk factor. It seems worthwhile to measure thyroid hormones in patients with unprovoked venous thromboembolic event and in contrarily the diagnosis of venous thromboembolism should be considered in patients with hyperthyroidism, particularly if additional prothrombic risk factors are present.

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EP1261

Atypical subacute thyroiditis
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Introduction
A diagnosis of subacute thyroiditis (SAT) is readily suspected when patients present with a particular set of typical clinical and laboratory characteristics. We present a patient with atypical SAT who had no neck pain but presented with fever, and weight loss; had thyrotoxicosis with normal 99mTc uptake, and needed higher doses of steroids to resolve.

Case report
A 57-year-old man presented with a fever (39 °C) of 2 month-duration. Physical examination was unremarkable. Laboratory analysis revealed WBC: 10 550 Krul, hemoglobin: 10 g/dl, erythrocyte sedimentation rate: 102 mm/h, C-reactive protein: 17 (<0.5) and normal renal, hepatic function tests. Epstein-Barr virus, and cytomegalovirus IgM and IgG titers were negative. Blood and urine cultures were also negative. Serum protein electrophoresis showed no abnormality compatible with multiple myeloma. Computed tomography of the neck, thorax and abdomen showed jugular, mediastinal, paraaortic and retroperitoneal lymph nodes in nonpathological size. Biopsy of a lymph node showed lymphoid hyperplasia. Transthoracic echocardiography did not show any finding compatible with infective endocarditis. TSH: 0.412 IU/ml (0.2–4.2), T3: 14 pg/ml (2.8–4.3), T4: 0.9 ng/dl (1.04–1.65), anti-TPO: 16 (0–34), anti-TG: 32 IU/ml (0–115), TSH receptor antibody: 0.4 U/l (<1.8), thyroglobulin: 14 ng/ml (0.83–68). Thyroid ultrasonography did not show any nodules. Thyroid scintigraphy showed normo-active, diffuse hyperplastic thyroid gland. Methimazole and propranolol were initiated. But his fever did not resolve until 60 mg of methylprednisolone was given with the diagnosis of SAT. After steroid treatment, T3 levels decreased which had increased previously with methimazol.

Conclusion
This case presented atypically in that he had no neck pain but was diagnosed with SAT while being worked up for the fever of unknown origin. Interestingly, he had normo-active thyroid gland and his T3 levels increased to very high levels in disproportion to his T4 levels. Higher doses of steroids were needed to resolve his fever and normalize his T3 levels. This report illustrates that the diagnosis and treatment of SAT can sometimes be difficult.

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EP1262
New treatments of diabetes: a promising alternative to bariatric surgery in obese patients
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Introduction
New treatments of diabetes improve global metabolic status beyond glycemic control and achieve weight reduction in many patients.

Case reports
We described four case reports to show GLP-1 agonists and dapaglifozin effects on metabolism and weight in patients with type 2 diabetes and obesity.

Case 1 (Liraglutide)
A 48-year-old man, hypertension, type 2 diabetes and extreme obesity. Baseline visit: treatment enalapril 20, acetylsalicyclic acid 100, metformin 850. Weight 191 kg, BMI 60.9 and HbA1c 6.6%. After 4 months under treatment with liraglutide: weight 158 kg, BMI 50.4 and HbA1c 5.3%.

Case 2 (Exenatide lar)
A 58-year-old man, type 2 diabetes and extreme obesity. Baseline visit: weight 141 kg, BMI 50 and HbA1c 6.7%. After 4 months under treatment with metformin 850 and exenatide lar: weight 127 kg, BMI 44.9 and HbA1c 5.5%.

Case 3 (Lixisenatide)
A 52-year-old woman, hypertension, type 2 diabetes and extreme obesity. Baseline visit: treatment metformin 850, simvastatin 20, losartan 100, atenolol 50. Weight 138 kg, BMI 55.4 and HbA1c 6%. After 4 months under treatment with metformin 850 and lixisenatide: weight 133 kg, BMI 47 and HbA1c 6%. After 10 months under treatment with metformin 850 and lixisenatide: weight 125 kg, BMI 48.8 and HbA1c 5.7%.

Case 4 (Dapaglifozin)
A 64-year-old man, type 2 diabetes, dyslipidaemia and grade 1 obesity. Baseline visit: treatment metformin 850 and simvastatin 40. Weight 106 kg, BMI 34.2 and HbA1c 8.8%. After 5 months under treatment with dapaglifozin: weight 93.6 kg, BMI 31.8 and HbA1c 6.6%.

Conclusion
GLP-1 agonists and dapaglifozin got significant improvement of anthropometric parameters and glycaemic control in patients with type 2 diabetes and obesity. They were safety and well tolerated, and could represent a promising alternative to bariatric surgery.

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EP1264
Severe hyponatremia in the course of autoimmune polyglandular syndrome type 2 of atypical clinical picture
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Introduction
Severe hyponatremia defined as the blood sodium concentration below 115 mmol/l is rarely recognised in the course of autoimmune polyglandular syndrome type 2 (APS L2). The aim of the paper is to present the female patient with severe hyponatremia preceding the diagnosis of APS L2 of atypical clinical picture.

Case report
A 54-year-old woman with the diagnosis of psoriasis established 10 years earlier and treated for psoriatic arthritis from 7 years. She was admitted to the emergency ward because of persistent vomiting, hyponatremia = 111 mmol/l and hyperkalaemia = 5.4 mmol/l. For several months she observed increasing fatigue, hypotension, recurrent abdominal pain, loose stools, increased appetite for salt, progressive darkening of the skin and weight loss of 12 kg/6 months. Her ACTH level was 857.3 pg/ml; blood cortisol in the morning was: 3.7; 1.6 µg/dl and in the evening: 2.7, 1.7 µg/dl. Lack of adrenal response after stimulation with Synacthen and normal adrenal CT image were confirmed. 21-hydroxylase autoantibodies were negative (1: <10). FT₃-32.3 pmol/l; FT₄-16.2 pmol/l; TSH <0.004 mIU/l. Antibodies antiTPO-4659 U/ml; antiTG-391 U/ml; TRAb-1.8 U/ml. USG revealed 12 ml thyroid gland with numerous, hypoechogenic, small (4 mm) areas in both lobes. The diagnosis of primary adrenal insufficiency with concomitant autoimmune thyroid disease with hyperthyroidism in a patient with psoriatic arthritis was established. Summary, Psoriatic arthritis and thyroid disease with thyrotoxicosis are rare components of APS type 2 and hyponatremia occurs more frequently in patients with concomitant hyperthyroidism.

Conclusion
Severe hyponatremia in our patient could be the result of a significant increase in demand for cortisol caused by thyrotoxicosis and the lack of opportunity to increase its production by the adrenal cortex.

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EP1265
Diabetes mellitus in a patient with Leri–Weill dyschondrosteosis
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Introduction
Leri–Weill dyschondrosteosis (LWD) is a rare autosomal dominant dyschondrosteosis characterised by Madelung deformity and mesomelic dwarfism. Majority of cases are associated with haplinsufficiency of the short-shaute homeobox-containing (SHOX) gene. Here we report a patient with LWD and diabetes mellitus (DM).

Case report
A 31 years old man applied with polyuria and polydipsia. He did not have any chronic disease. In family history, father had type 1 and mother had type 2 DM. His height was 146 cm and weight was 62 kg, with a BMI of 29.1 kg/m².

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Laboratory investigation revealed a fasting blood glucose of 298 mg/dl, HbA1c 13.4%, insulin 8 μU/ml (2.6-24.9), C-peptide 1.65 ng/ml (0.1-3.6). AntiGAD, anti-insulin and islet-cell antibodies were negative. Intensive insulin treatment was started. The result of genetic analysis made to determine cause of short stature about 1.5 years ago was 45,X,-Y15[46,X,der(Y)(Y;Y)p11.2;q11.21). There was deletion in the SHOX gene of Y chromosome. He had bilateral Madelung deformity which is an epiphyseal growth plate disturbance characterized by shortened and bowed radius and ulnae leading to dorsal dislocation of the distal ulna. Thus, he was diagnosed to have LWD.

Conclusion
Haploinsufficiency of the SHOX gene which is located on the pseudoautosomal region of both the X- and Y-chromosomes is a cause of short stature in various clinical conditions including LWD. There are previous reports indicating inverse association between height and diabetes, and showing increased prevalence of gestational DM in patients with short stature. In the literature, clinical features of LWD is limited to skeletal anomalies and short stature. This is the first report of DM in a patient with this syndrome. Although, it is probable that this might be just a coincidence, we think possible association between impaired glucose metabolism and syndromes related with short stature needs further investigation.

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Hyponatraemic encephalopathy induced by single dose of indapamide
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Introduction
Hyponatraemia is the most common of electrolyte abnormalities. There are numerous factors which may directly cause or contribute to hyponatraemia, including dehydration, concomitant cardiac/hepatic/renal disease, and certain medications, such as diuretics. Hyponatraemia may cause a range of symptoms, depending on the speed and severity of the deficiency. Mild hyponatraemia (＞115 mmol/l), can cause malaise, nausea and vomiting. Significant hyponatraemia, [Na+]＜115 mmol/l, manifests with confusion, seizures, and ultimately coma. Chronic, ‘asymptomatic’ hyponatraemia has been shown to cause gait disturbances, falls and neurocognitive impairment.

Case
A 76-year-old lady was brought into A&E, having been found collapsed at home. GCS was 6/15. She was confused and agitated. She was euvoalaemic, and had normal blood glucose. CT-head showed no acute intracranial abnormality. Mild hyponatraemia (108 mmol/l), can cause malaise, nausea and vomiting. Significant hyponatraemia, [Na+]＜115 mmol/l, manifests with confusion, seizures, and ultimately coma. Chronic, ‘asymptomatic’ hyponatraemia has been shown to cause gait disturbances, falls and neurocognitive impairment.

Laboratory work up showed a profound hyponatraemia, Na+ 108. Prior to this admission, her sodium levels were within normal ranges. Full-body CT scan, which showed no neoplastic cause for her hyponatraemia. Her past medical history also included asthma, IHD, and primary hypothyroidism. She was smoker, although she denied any new respiratory symptoms, or weight loss. She reported having commenced indapamide for hypertension one day prior to presentation.

Laboratory work
K+ 4.2 mmol/l; corrected calcium 2.13 mmol/l, TSH 9.9 mU/l, FT3 18 pmol/l. Her urinary osmolality was 475 mOsml/kg; urinary [Na+] was 27; serum osmolality, 236, serum cortisol was 761 nmol/l. Indapamide was stopped and she was put onto fluid restriction, with a strict input/output chart. She had regular [Na+] checks, which showed gradual improvement in the hyponatraemia to 108 mmol/l on day 0, 111 mmol/l on D1, 120 mmol/l on D2, 127 mmol/l on D3. She was notably less confused and agitated on discharge, and, when reviewed in clinic a 4 weeks later, her symptoms had resolved entirely. More recent biochemistry shows normal sodium.

Conclusion
Diuretics are associated with hyponatraemia. However this is the first reported case of hyponatraemia and encephalopathy after single dose of indapamide.

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Noninfectious but genetic bilateral neck swelling
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Introduction
We describe a case of a 32 year old woman with bilateral carotid body tumours as initial finding of a paraganglioma syndrome type 1.

Case
A 32-year-old previously healthy mother was referred because of bilateral neck swelling, presumably lymphadenopathy, associated with recurrent upper respiratory tract infections during the past year. Cervical ultrasound raised the suspicion for bilateral carotid body tumours which were confirmed by MR-imaging and a subsequent DOPA-PET-CT, which showed no evidence for multicentricity or metastases. Plasma metanephrines including methoxytyramine were within the normal range and although a family history was negative, the genetic work-up revealed a SDH mutation (paraganglioma syndrome type 1).

Discussion:
HNPGLs are rare tumours (incidence 1:30 000 – 100 000) derived from extraadrenal chromaffin cells and 95% arise from the parasympathetic nervous system, typically the carotid body (glomus caroticum), jugular bulb (glomer jugulare) and different branches of the vagal nerve (glomus vagale, nervous typanicum). Plasma methoxytyramine may be elevated (1/3 of cases), normally they are clinically nonsecretory and present because of their mass effects. Around 35% are associated with a genetic defect, with SDH-mutations accounting for >50%, SDHB for 20-35% and SDHC for 15% (extraordinary SDHAF2). The inheritance pattern is autosomal dominant for SDHs mutations, but in SDHD and SDHAF2 maternal imprinting is postulated. Malignancy is rare (3.5%) although metastasizes occur up to 20 years after initial diagnosis. Staging is performed by functional imaging with 18F-DOPA- or 11C-DOTATATE-PET-CT, anatomical imaging with CT and/or MRI gives a better locoregional resolution. Surgical resection may be associated with significant morbidity especially caudal cranial nerve injury. Radiomiodic-therapy or radiotherapy/-surgery must be evaluated as alternatives. Genetic counselling and testing is mandatory due to the high rate of germline mutations and familial disease.

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Noninfectious but genetic bilateral neck swelling
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Introduction
Noninfectious but genetic bilateral neck swelling
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EP1269
The association between Graves’ disease and thyroid cancer: coincidence or causality? Case report
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Introduction
Graves’ disease (GD) has been related to a higher incidence of thyroid cancer. Thyroid nodules found in GD seem to have a higher risk for malignancy. The prognosis of thyroid cancer may be aggravated by the association with GD.

Case report
We present the case of a 56-year-old woman diagnosed with multinodular goitre and overt hyperthyroidism for which therapy with carbimazole 40 mg/day was started. She was referred to our Endocrinology Department 2 months later for follow-up. She complained of important weight loss, palpitations, fatigability and recent swelling of the neck. Clinical examination revealed a painless large goitre and mild exophthalmia. Laboratory findings still showed subclinical hyperthyroidism (TSH=0.013 μIU/ml – normal range 0.4–4 and FT4 = 0.957 ng/dl – normal range 0.89–1.76). TSH antibodies (TSAb) were present in high titres and GD diagnosis was established. Thyroid ultrasound revealed a large conglomerate mass with microcalcifications in the left lobe on the background of a hypoechogenic, hypervascular goitre. FNAB from the nodule revealed cytology highly suspicious of malignancy. Total thyroidectomy was performed and histopathology report showed invasive papillary thyroid carcinoma follicular variant and typical findings of GD. After surgery, the patient underwent radioactive iodine (¹³¹I) therapy. The post-therapy whole-body radionuclide scan showed remnant thyroid tissue and multiple iodine-avid lung metastases. Thyroglobulin levels remained abnormally elevated, making the patient a candidate for an additional radioactive iodine administration.

Conclusions
This is a rare case of simultaneously diagnosed GD and thyroid carcinoma. The tumour had a rather invasive and aggressive phenotype, in contrast to histopathology and in accordance with studies proposing GD as a negative prognostic factor in thyroid cancer. We suggest managing patients with thyroid cancer and GD according to high-risk protocols. We recommend a closer ultrasound follow-up for nodules in GD and the performance of FNAB when nodules are found.

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EP1270
Severe hypocalcaemia and hypomagnesaemia secondary to omeprazole
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Introduction
Proton pump inhibitors (PPIs) are commonly prescribed drugs. We report a case of severe hypocalcaemia secondary to omeprazole-induced hypomagnesaemia.

Case report
A 56-year-old Chinese man was admitted to hospital in Jun 2014 with vomiting and weakness. On admission, he was severely hypocalcaemic (adjusted calcium 1.37 mmol/l (REF: 2.15–2.58)) and hypomagnesaemic (Mg 0.1 mmol/l (REF: 0.7–1.0)). Serum phosphate and 25-OH vitamin D levels were normal. Intact PTH done after normalisation of serum magnesium showed secondary hyperparathyroidism (intact PTH 61.0 pmol/l (REF: 0.8–6.8)). An inpatient endocrinology referral was made for persistent hypocalcaemia. Review of his medical records revealed initiation of omeprazole in 2010 for peptic ulcer prophylaxis when he was prescribed short course prednisolone for gout. Omeprazole was continued after prednisolone cessation. Severe hypomagnesaemia and hypocalcaemia was also noted during two previous admissions to another hospital in Nov 2013 and Jun 2014. Calcium levels were normal between hospitalisations but magnesium levels were not rechecked. In view of the possibility of omeprazole induced hypomagnesaemia and hypocalcaemia, omeprazole was stopped and changed to famotidine. With electrolyte replacement and a short course of calcitriol, serum calcium normalised within 4 days and remained normal at follow-up with calcium carbonate 1.25 g bd (as a phosphate binder) and no magnesium supplementation.

Conclusion
Severe hypomagnesaemia with hypocalcaemia is a rare side effect of PPI use. PPI use may alter intestinal absorption of magnesium, resulting in hypomagnesaemia, which then in turn impairs PTH secretion and action, causing hypocalcaemia. Correction of magnesium levels by stopping the PPI and aggressive magnesium replacement is hence essential before correction of the hypocalcaemia can be achieved. It is therefore important to have a high index of suspicion for this potentially life threatening side effect in patients on omeprazole presenting with hypocalcaemia.

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EP1271
Late-diagnosed primary hyperparathyroidism resulting in loss of kidney and advanced osteoporosis
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Introduction
The report describes the case of a late-diagnosed primary hyperparathyroidism in the patient, who developed catastrophic renal complications and such advanced osteoporosis, that hungry bone syndrome occurred after removal of parathyroid adenoma.

Case report
A 63-year-old woman with long-lasting nephrolithiasis was admitted to the hospital due to high PTH discovered in a routine laboratory testing. She had undergone left-side nephrectomy 2 years before admission due to hydronephrosis. In the last year she lost 5 kg and suffered from asthenia, joint-pain and recurrent infections of the urinary tract. Laboratory tests during hospitalisation confirmed significantly raised PTH (2070 pg/ml, ALP (1047 IU/l), total calcium, and ionized serum calcium (3.26 and 1.91 mmol/l respectively). Also, anaemia (Hb, 8.8 g/l) was observed and serum creatinine was substantially deteriorated (2.12 mg/dl, GFR 19 ml/min). Calcium (92.4 mg) and phosphate (367 mg) urine excretion in 24 h collection and 25(OH)D3 (17 ng/ml) were under normal range. Neck ultrasonography demonstrated multinodular goitre (thyroid function tests were normal). The biggest nodule was in the right thyroid lobe, it was hypoechogenic and had 20 × 16 × 24 mm diameter. 99mTc-sestamibi scintigraphy detected abnormal lower right parathyroid gland. DXA osteodensitometry showed advanced osteoporosis (~4.8 s.d. lumbar and ~3.6 s.d. femoral neck T-score). During the parathyreoidectomy rapid decrease of serum PTH was observed (to 150 pg/ml). Two months postoperatively patient developed hypocalcaemia (1.93 mmol/l) and again high level of PTH (946 pg/ml). The diagnosis of hungry bone syndrome was made. The treatment with vitamin D, calcium supplementation, and alendronate sodium was started, which resulted in a gradual decrease in PTH and normalization of serum calcium.

Conclusion
In each case of nephrolithiasis the probability of hyperparathyroidism should be checked, otherwise it can lead to irreparable damages of human organism.

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EP1272
Acute thyroiditis due to nocardia associated to thyrotoxicosis
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Introduction
Acute thyroiditis is an uncommon illness that exceptionally presents with thyrotoxicosis. Differential diagnosis mainly includes subacute thyroiditis. Nocardia asteroids is an opportunistic pathogen, with the majority of infections occurring in immunocompromised patients, as the delay in diagnosis due to negative blood cultures makes it potentially lethal.

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Case report

We present a case of acute thyroiditis due to Nocardia that received a kidney cadaveric renal transplant. A 44-year-old woman with diabetic nephropathy had a cadaveric renal transplant. About 3 months later, she presented neck pain accompanied by fever, dysphagia, enlargement of thyroid gland and thyrototoxicosis. These findings together with image tests were consistent with subacute thyroiditis. However, worsening of symptoms despite usual treatment and the finding of an abscess in the ultrasonography study made us formulate the possibility of an acute thyroiditis. Fine-needle aspiration of the abscess and drainage were performed and Nocardia asteroides was isolated in the fluid culture. Owing to abscess persistence despite of drainage and specific antibiotic therapy surgical thyroidectomy was made.

Conclusions

Acute thyroiditis due to Nocardia is exceptional, with only six published cases in the literature, none of them presenting with thyrototoxicosis. It is the second known case of Nocardia thyroiditis in a patient with solid transplant organ, being the rest in patients under corticosteroids treatment. Nocardiosis is typically regarded as an opportunistic infection occurring in immunocompromised hosts and is it to be taken into account in these patients.

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**Adrenal embolisation in severe ectopic Cushing: unusual case and extraordinary measures**

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Introduction

Pancreatic ACTHomas have a poor prognosis with severe and rapidly progressive clinical courses, influenced by hypercortisolaemia thus whenever possible, control of the cortisol levels should be obtained to reduce complications. We report the use of adrenal embolisation in a case of a life threatening paraneoplastic Cushing.

Case

A 51-year-old woman with a negative past medical history complained of general weakness. Cushing’s syndrome was suspected on the basis of hypokalaemia, new onset hyperglycaemia and metabolic alkalosis found in the laboratory tests run on admission. She had no Cushingoid features except mild plethora. The suspicion was confirmed by high levels of urinary free cortisol, serum cortisol and ACTH, a lack of circadian rhythm of serum cortisol, and a low (1 mg) and high dose (8 mg) overnight of dexamethasone tests that failed to suppress. CT and whole body PET scan showed 2 x 3 cm mass in the pancreas tail. She underwent the excision of the pancreatic mass and pathology confirmed the neuroendocrine nature of the tumour. Cushingoid features were more obvious and liver metastases were observed so treatment with ketoconazole was started, initially decreasing cortisol levels, but refractory hypercortisolaemia recurred although dose was increased and metopirone added. The patient became psychotic so mifepristone was commenced, but she continued to deteriorate. It was therefore decided that an attempt should be made for bilateral adrenalectomy, but the patient was unfit for surgery so a bilateral adrenal embolectomy was performed. A week after the procedure her condition improved and the urinary cortisol levels lowered. Unfortunately the patient died soon after due to a multiorgan failure.

Conclusions

Aggressive attitudes to control cortisol levels are necessary to reduce comorbidities in ectopic Cushing. This case shows that adrenal embolectomy might be of some use when the patient has become unfit for surgery and in whom medical therapy has failed.

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**Primary hyperparathyroidism in pregnancy**

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Introduction

Hyperparathyroidism during pregnancy is a serious problem. Appropriate management is a matter of debate. We would like to present cases in which, PHP was diagnosed in completely different circumstances, though end up with various pregnancy outcomes.

Case report

First patient was 29-year-old women in 21th week of her second pregnancy admitted to our ward due to suspected relapse of Graves’ disease and possible adrenal dysfunction. She presented with weakness, abdominal pains, vertigo in 7th week of pregnancy. During hospitalisation, previous suspicions were ruled out. Unexpectedly, we discovered elevated concentration of total calcium. After thorough examination, we confirmed a diagnosis of hyperparathyroidism. Owing to biochemical deterioration she was operated in 24th gestation week. The women gave birth to a healthy baby girl in 40th week of gestation. Second patient was 28-year-old women admitted to Outpatient Endocrinology Clinic due to hypercalcemia. Medical history revealed miscarriage in 9th week. During pregnancy which she lost, calcium levels were very high. On the day of visit neck ultrasonography depicted a hypoechoic region which could be consistent with enlarged parathyroid gland. She was operated. Frozen section pathology and intraoperative PTH assay confirmed diagnosis of parathyroid adenoma and curative procedure.

Conclusion

Presented cases highlight the importance of controlling calcium-phosphate balance in pregnancy. Decisions concerning method of treatment PHP are difficult. When conservative procedures are introduced, mother and her child should remain under strict control. On the other hand operation during pregnancy is hazardous. Our experience gives a novel insight into that complicated problem. Taking into account possible adverse effect of PHP on health of both women and fetus there are growing evidence pro surgery, regardless of gestational age.

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**Thyroid tuberculosis mimicking carcinoma: case report**

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Tuberculosis of the thyroid gland occurs rarely, and should be considered in the diagnosis of nodular lesion of the thyroid gland. We report the case of a 44-year-old woman admitted for therapeutic management of a suspected goiter appeared at 2 months of hospitalisation and quickly increasing in volume in a few days, she had a goiter clinically type 2, firm, homogeneous, without palpable nodules in it, hardly moving with swallowing movements with slight dysphagia without signs of thyroid dysfunction. Cervical ultrasound: found a suspicious mass in the right thyroid 1. FNA of cervical mass found the CPE side for a very granulomatous thyroiditis DeQuervain IDR A. A Tuberculin had regained energy. The patient received a total thyroidectomy before the signs of malignancy on ultrasound. Histology was in favor of a histopathology of thyroid and thyroid localization soft tissue died a Caseo folliculaire.mise tuberculosis TB treatment with good clinical course.

Conclusions

Thyroid tuberculosis is a rare disease, which can take various forms, especially you must think in TB endemic area, the diagnosis is histological and/or bacteriological. Treatment is primarily medical, based on a combination of anti tuberculosis. Preoperative diagnosis of thyroid tuberculosis is important because of the availability of medical treatments and the limited role of surgery.

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**Case report: superior vena cava syndrome secondary to intrathoracic goitre**

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Clinical and hormonal characteristics of a series of patients affected by inappropriate TSH syndrome: insights into the differential diagnosis

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Introduction
Normal or elevated TSH level in the presence of elevated T4 is defined as ‘inappropriate TSH syndrome’. Two main clinical conditions that can lead that syndrome are TSH-secretting adenoma (TSHoma) and resistance to thyroid hormone (RTH). Making the correct diagnosis is crucial in order to decide the most appropriate treatment option. Herein we presented clinical and laboratory data of seven patients who were hospitalised for the differential diagnosis of the two clinical entities.

Method
Our database was reviewed for the patients diagnosed with inappropriate TSH syndrome at our hospital between 2010 and 2014. After exclusion of the other rare causes of inappropriate TSH syndrome, seven patients who were hospitalised for the differential diagnosis of TSHoma and RTH were included in this report.

Result
Age of the patients was changing between 20 and 52 years. Clinically two patients were asymptomatic, three had tachycardia and weight loss and one had goitre. Final diagnosis was RTH in four patients, TSHoma in two and unequivocal in one. Two patients diagnosed with TSHoma were operated and had positive staining with TSH. Both of the TSHoma cases had macroadenoma on pituitary MRI and visual field defect while two of four patients with RTH had microadenoma. Alpha-subunit/TSH molar ratio was above 1 in all patients diagnosed with TSHoma while it exceeded 1 in two patients with the final diagnosis of RTH. TRH stimulation test revealed a blunted response in all patients with TSHoma and a positive response (increase > 100%) was observed in all with THR. TSH was suppressed after T4 suppression test in all patients with the final diagnosis of RTH.

Conclusion
Differential diagnosis of RTH and TSHoma can be a clinical challenge and requires complex hormonal tests and imaging methods. Since incidental pituitary tumours are not rare, presence of an adenoma should not rule out diagnosis of RTH.

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EP1278

Autoimmune polyglandular syndrome: case report series

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Introduction
The polyglandular autoimmune syndromes (PAS) are rare conditions characterised by the failure of several endocrine glands sometimes associated with other non-endocrine autoimmune diseases. There are four categories of PAS: PAS-I includes at least two out of: mucocutaneous candidiasis, hypoparathyroidism and adrenocortical failure. PAS-II comprises of Addison’s disease, autoimmune thyroid disease and/or type 1 diabetes (Carpenter’s syndrome). PAS-III is defined by the presence of other autoimmune disorders than Addison’s disease and hyperparathyroidism, while PAS IV includes non-endocrine autoimmune disorders and Addison’s disease, but not hypothyroidism.

Case reports
We present three cases of a larger series of PAS type IIIB. The first is of a 55-year-old woman, who was diagnosed with PAS-II (Addison’s disease, autoimmune thyroiditis and latent autoimmune diabetes in adults). The second case is of a 42-old man, so far diagnosed with Basedow’s disease, type 1 diabetes and vitiligo. The third case is of a 22-year-old woman, diagnosed with type 1 diabetes mellitus and primary hypothyroidism so far. The occurrence of autoimmune diseases can continue in the latter two cases, therefore PAS-III could evolve into PAS II.

Conclusion
We underline the importance of screening for PAS after the first autoimmune disease is diagnosed. The key to successfully managing patients with PAS is to identify and treat their disorders early before complications occur. This may be achieved by early screening for autoantibodies or subclinical endocrine failure. Patients should be educated to comply with the lifelong medical surveillance and encourage their family members to be screened for autoimmune diseases as about 50% of patients with PAI II have siblings with autoimmune diseases.

Disclosure
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EP1279

Similia simillibus curentur: a novel treatment approach in endocrinology?

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Introduction
Hyperinsulinism hypoglycemia after gastric bypass surgery is a rare but probably underestimated complication. The mechanisms leading to hypoglycemia are complex and incompletely understood and involve several factors: A part from decreasing insulin resistance, caloric restriction and alteration of nutrient delivery, enhanced secretion of insulin and incretins (GLP1 and GIP), altered physiology of other hormones and dysregulation of counterregulatory effectors seem to play a major role. Treatment strategies include nutritional counselling with carbohydrate restriction and various medical treatments. Partial pancreatectomy is reserved for severe treatment-refractory cases.

Case report
A 53-year-old woman presented with postprandial hypoglycemia and neuroglycopenia 3 years after Roux-en-Y gastric bypass. A CGMS over 1 week demonstrated several hypoglycemic episodes typically occurring 2–3 h after meals. Endogenous hyperinsulinism was documented in a mixed meal test which was stopped after 2 h when the patient had severe neuroglycopenic symptoms and a plasma glucose of 1.9 mmol/l.1FL-DOPA-PET showed diffuse uptake within the pancreas but no focal enhancement. Despite carbohydrate restriction the patient continued to have neuroglycopenic symptoms. Diazoxide was begun but had to be withdrawn due to side effects. After discussion of other treatment options, the patient was started on liraglutide (Victoza) which was titrated to a dose of 1.2 mg daily. Frequency and severity of postprandial hyperinsulinemic hypoglycemia decreased markedly and neuroglycopenia resolved completely.

Conclusions
GLP1 analogues might be a new treatment option for hyperinsulinemic hypoglycemia after bariatric surgery. However, the exact mechanism of action remains to be elucidated. It can be assumed that a stimulation of glucagon secretion with concurrent inhibition of insulin secretion in low blood glucose.

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states by GLP1 analogues partly explains the stabilising effect on glucose metabolism in these patients. Nevertheless, further studies are needed.

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**EP1280**

**The use of omega-3 free fatty and medium chain triglycerides in combination with GLP1 and SGLT2 in the management of obesity and severe refractory hypertriglyceridaemia**

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Hypertriglyceridaemia and obesity are common encounter in diabetic patients. It is often refractory to conventional treatment especially those with a very high triglyceride (TG) levels. The institution of medium chain diet (MCT) and fish oil in addition to the liraglutide and SGLT2 and conventional insulin has rendered significant and a satisfactory triglyceride, and glucose level as well as weight reduction. We would like to illustrate a case of 35 years old lady with a different treatment modality apart from the current general approach in managing obesity and hypertriglyceridaemia. There was marked reduction in HbA1c, 12.6 to 9.2% within 2 months. This is accompanied with weight reduction of 6 kg within four months. While the triglyceride levels steadily decreasing from 32.3 to 3.18 mmol/l and remained so throughout the treatment. There was no side effect observed at this period of treatment.

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**EP1281**

**Multiple endocrine organ failure due to amyloidosis**

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Introduction

Amyloidosis is characterised by accumulation of amorph and proteinous substance in several tissues and organs. Thyroid, adrenal, and pituitary insufficiencies may rarely be observed due to accumulation of these substances. Here, we present a case to point out this rare condition.

Case report

A 19-year-old male patient admitted with complaints of swelling in the neck, abnormality in thyroid hormone levels and fatigue. He had been diagnosed with familial Mediterranean fever at the age of 5. At 13 years old, he had renal insufficiency due to amyloidosis and had undergone renal transplantation. Physical examination revealed systemic arterial blood pressure of 90/60 mmHg, pulse rate of 72 beats/min. Thyroid gland was found to be diffuse palpable (grade 2), secondary sex characteristics development was defined as stages 2–3. In laboratory evaluation, TSH level was elevated, FT4 level was decreased, anti-TPO and anti-TG were negative. He had primary adrenal insufficiency and hypogonadotropic hypogonadism. ACTH and GnRH stimulation tests were in concordance with primary adrenal failure and hypothalamic hypogonadism.

**Conclusions**

Systemic amyloidosis may be accompanied with amyloid accumulation in thyroid gland as well as adrenal and pituitary insufficiencies. Thus, endocrinologic evaluation is necessary in these patients.

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**EP1282**

**Gynaecomastia in a patient with von Recklinghausen’s disease (neurofibromatosis type I)**

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Introduction

Neurofibromatosis type I (NFI), also known as von Recklinghausen’s disease, is the most common type of NF and one of the most frequent human genetic diseases. Gynaecomastia due to pseudoanomalous stromal hyperplasia (PASH) in patients with NFI is quite a rare complication but still it should be differentiated from gynecomastia caused by other conditions.

Clinical case

A 30-year-old man, previously diagnosed with NFI at the age of 19, was first consulted in the Endocrinology department of MSMU in March 2014. He complained bilateral enlargement of breasts, painful feeling in them, weight loss, reduction of libido, muscle weakness, back pain and pain in the legs, diarrhoea. Physical examination: height 165 cm, weight 42.5 kg, BMI 15.7 kg/m², strong reduction of subcutaneous fat, breasts enlarged, painful while palpated; loss of facial hair, multiple neurofibromas in supraclavicular, axillary, and parotid areas. Laboratory analysis: serum creatinine 50.8 mmol/l (62.0–115.0), prolactin 136.0 mIU/ml (47–135), macroprolactin 61.0 mIU/ml, estradiol 97.0 pmol/l (0–146), testosterone 9.7 nmol/l (8.4–28.7), and leptin 0.9 ng/ml (2.5–6.6). DXA: generalized osteoporosis (Z-criteria – 3.2 to –3.8), Total body quantitation: total fat tissue 9.9%. Immunological tests of specific antibodies in celiac disease: negative. Brain MRI: no signs of a pituitary adenoma. Breasts US: gland tissue hyperplasia, ducts are not dilated, no cysts or tumours were detected. Medianistin lymph nodes biopsy: neurofibromas. Spine CT, MRI: multiple neurofibromas. Neurologic status: Multiple compressive-ischemic mononeuropathies of upper and lower limbs, distal asymmetric tetraparesis, neuropathic pain syndrome, crampy. Pain syndrome is treated successfully with pregabaline 375 mg/day and amitriptyline 0.05 mg/day. A bilateral mastectomy was performed at June 2014. Osteoporosis is treated with zoledronic acid and combined preparations of calcium and vitamin D3.

**Conclusion**

We report our experience of gynecomastia and hyperprolactinaemia in a patient with NFI. Though these are rare complications of the disease, if found, such patients should undergo complex examination to exclude other causes of this state, which can worsen the course of their primary disease.

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**EP1283**

**Petrifried ears associated with Schmidt’s syndrome**

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Introduction

Bilateral calcification of auricular cartilage is an uncommonly reported condition. The aetiology of this phenomenon is still unclear. Petrifried ears have seldom been described in association with endocrinopathies such as adrenal insufficiency, hypothyroidism, diabetes mellitus, and acromegaly.

Case report

We present the case of a 42 year-old male patient, diagnosed with Addison’s disease at the age of 14, currently undergoing treatment with prednisone 10 mg/day, with low compliance and therefore repeated episodes of adrenal crisis throughout the years. At the age of 42 he was diagnosed with hypothyroidism due to Hashimoto’s thyroiditis and treatment with levothyroxine 25 μg/day was initiated. Physical examination revealed hyperpigmentation of the skin, lipoma of the posterior chest wall, markedly rigid auricular cartilages that were difficult to fold manually, with no evidence of hearing impairment. CT scan confirmed bilateral calcification of the auricular cartilages.

**Conclusions**

A long history of poorly controlled adrenal insufficiency (in this case more than 25 years) and the presence of primary hypothyroidism seem to be precipitating factors for auricular calcification.

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**EP1284**

**Two cases of bullous pemphigoid induced by vildagliptin**

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Background

Bullous pemphigoid is an autoimmune blistering disease that commonly arise in elderly with increased risk for mortality and morbidity. The aetiology of this disease is not entirely clear, although a few cases have been described with dipeptidyl peptide IV inhibitors.

Case 1

A 81-year-old man presented with bullous pemphigoid after 28-month treatment with repaglinide, vildagliptin, and metformin. The patient’s condition didn’t improve with local treatment with clobetasol. The patient was started on methylprednisolone and azathiopurine but skin lesions sustained. Remission was achieved only after withdrawal of glitin.

Case 2

A 64-year-old man treated with insulin glargine, insulin aspart, and vildagliptin for 12 months presented with bullous pemphigoid on skin and laryngeal mucosa. After discontinuation of vildagliptin skin lesions were resolved but laryngeal involvement continued. Mucosal lesions were resolved after methylprednisolone and azathiopurine treatment.

Conclusion

In the literature, there have been few cases described with glitins. The exact mechanism has not been known but believed to be modified immune responses. These reports support the risk of bullous pemphigoid in patient exposed to glitins. The difference of our cases from the literature is mucosal involvement and remission of our cases only with immunosuppressive agents.

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**EP1285**

**Hashimoto’s thyroiditis with subclinical hypothyroidism, but severe growth delay in a prepubertal boy**

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Hashimoto’s thyroiditis is an autoimmune condition most common in females but can be also found in children with a prevalence of 1.2%. When is associated with hypothyroidism, the growth delay is an important, but late symptom. We present the case of a 12-year-old boy presenting with small height for age (123 cm, –3 S.D.), important weight gain and fatigue. He was the only child from parents of average height and had normal weight at birth (3300 g). Growth delay was not obvious until 2–3 years ago, when the child remained the shortest in the class, growing at a pace of <2 cm/year. Although with an IQ above average, the patient had mild features of hypothyroidism. Clinical supposition was confirmed by laboratory investigation: $fT4 = 0.3 ng/ml$ (normal 0.9–1.9 ng/ml) and $TSH = 35 mIU/l$ (normal 0.4–6 mIU/l). Endocrinological examination of atrophic Hashimoto’s thyroiditis was set by high titer of anti-peroxidase antibodies – 326 U/l (positive when >50 U/l) and small, hypoechogenic, avascular thyroid gland. Therapy with 100 μg/day l-thyroxine and daily RGH injections (0.035 mg/kg per day) was initiated, with spectacular catch-up growth of 30 cm in 2 years (153 cm at 13 years, –0.8 S.D., corresponding to adult parental height).

Hashimoto’s thyroiditis is a frequent disease in adult women, but seldomly encountered in prepubertal boys. Normal intellect, relatively harmonious development and the presence of the thyroid gland excluded the hypothesis of an undiagnosed congenital myxoedema in our case. Diagnosis was mainly set by severe growth delay. Catch-up growth under thyroid hormone substitution does not completely restore height handicap in long-standing hypothyroidism, therefore the association of GH therapy may be beneficial, as in our case.

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**EP1286**

**A case of childhood autoimmune polyglandular syndrome type 1**

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Autoimmune polyendocrine syndromes (APS) are rare groups of diseases with autoimmune failure of at least two endocrine glands. In general, APS1 first occurs with candidiasis. Hypoparathyroidism generally presents until 10 years of age, and adrenal insufficiency around 20 years. We aim to report a young girl is presented with early onset APS1 first presenting with adrenal insufficiency.

Mucocutaneous candidiasis on the oral mucosa, and ectodermal dystrophic changes in her nails attracted attention in an 18-year-old girl in asthenic appearance who attended the Endocrinology Outpatient Clinic for malaise and failure to thrive. No hyperpigmentation was detected on the skin and mucosa on physical examination because she took corticosteroid treatment. Pubertal development was accordant with Tanner stage 5. Other systemic examinations were normal. It was learned from her anamnensis that malaise, loss of appetite, darkening in skin colour, and changes in the nails were first detected and investigated at a Paediatrics outpatient clinic she attended when she was 6 years old. As much as learned from her records at that time, her height and weight were consistent with her age, turgor was decreased, the skin was dry, there were marking, shape and color changes in the hand nails, candidiasis and skin hyperpigmentation were detected. As PTH was 2.83 pg/ml (15–65), ACTH was 1250 pg/ml (7.2–63.3), and basal cortisol was 1 μg/dl (6.2–19.4), and there was no response to Synacthen stimulation test. Adrenal insufficiency, hypoparathyroidism, and candidiasis were detected and the patient was diagnosed for APS1.

Conclusion

APS1 clinically include a quite broad group of diseases. When one type of endocrinological disease is detected in a patient, the patient should be tested for complete blood count, electrolytes, hormonal levels, and antibodies for other diseases once every 3 years.

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**EP1287**

**Propylthiouracil-induced hepatotoxicity in Graves’ disease: a case report**

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Introduction

Propylthiouracil-induced severe hepatotoxicity is a relatively rare occurrence, with very few cases reported in the literature. The management of this complication in pregnancy can be a challenge because of the effects of the various treatment options on the foetus.

Case presentation

We report a case of hyperthyroidism in a 28-year-old woman that occurred at 20 weeks gestation. This situation was due to Graves’ disease. Propylthiouracil treatment was used. The following of the pregnancy doesn’t show any side effects. 15 days after delivery, she has a vomiting and fatigue. Check list show elevated ALAT=1000 U/l. This liver toxicity has been managed by stopping this medication. After 4 days, ALAT remain to normal rate.

Conclusion

This case illustrates a rare complication of treatment with a presumed safe drug during pregnancy followed by adverse maternal outcomes due to the hepatotoxicity treatment.

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EP1288
Combined treatment with sitagliptin and vitamin D in a patient with latent autoimmune diabetes of adulthood

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Objective
To report a case of a patient diagnosed with latent autoimmune diabetes of adulthood (LADA) based on clinical presentation and positive glutamic acid decarboxylase antibodies (GAD-abs) that converted to antibody negative diabetes after combined treatment with sitagliptin and vitamin D.

Methods
A 31-year-old male presented at the emergency room with symptoms of polyuria, polydipsia, and weight loss. Blood glucose was 300 mg/dl with mild ketonuria and HbA1c was 9.6%. The patient had a family history of autoimmune disorders. Declining insulin therapy he was initially treated with glargide and metformin. Owing to the patients poor glycemic control a GAD-abs titer measurement was performed and the results came back positive at 32 U/ml (NV < 5 U/ml), so a LADA diagnosis was established. Other blood tests came back normal except from a low 25-OH-vitD level of 11 ng/ml (NV > 30 ng/ml). Declining insulin therapy, he was advised to discontinue glargide and a combination of metformin 850 mg/sitagliptin 50 mg twice daily along with vitamin D supplementation (2000 IU/day) was prescribed.

Results
At follow-up visits, his HbA1c was 6.1% at 6 months and 5.4% at 11 months. His GAD-abs level declined by 86% within normal range at 4.2 U/ml. Two years later, receiving the same treatment, he has negative GAD-abs, has HbA1c is 5.2% and he maintains an excellent glycemic profile.

Conclusion
Both vitamin D analogues and dipeptidyl peptidase 4 (DPP4) inhibitors have been shown to improve β-cell function and attenuate autoimmunity in type 1 diabetic mouse models. To our knowledge this is the first case that combined treatment with sitagliptin and vitD in a patient with LADA reverted the phenotype and preserved an excellent glycemic control without the use of insulin 24 months after diagnosis.

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EP1289
A rare case of papillary thyroid carcinoma and MALT thyroid lymphoma in the setting of Hashimoto’s thyroiditis

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Introduction
Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy (80%), while primary thyroid lymphomas (PTLs) occur in only 0.6–5% of cases. A significant number of PTCs, as well as PTLs, arise in the setting of Hashimoto’s thyroiditis (HT), however the simultaneous occurrence of these two malignancies is extremely rare.

Case report
We present a 34-year-old female patient with thyroid MALT lymphoma and coexisting papillary microcarcinoma (PMC) in the setting of HT in the contralateral lobe that was admitted to our Institution for thyroid surgery. Patient had no compressive symptoms or lymphoma-related symptoms. Physical and ultrasonical examination in our Institution showed euthyroid multinodal goitre with pre-laryngeal medial neck mass (position of pyramidal lobe) and negative regional lymph nodes. Additionally, patient had increased antibodies’ level. Preoperative fine-needle aspiration biopsy of pyramidal lobe tumour showed HT. Patient was submitted to total thyroidectomy with sentinel lymph node biopsy of jugulo-carotid regions after 1%–methylene blue dye injection. Histopathology analysis showed MALT lymphoma in the right lobe and HT with incidental PMC in the left lobe. Lymph nodes were diagnosed as benign, with reactive sinus histiocytosis. Postoperative whole body scintigraphy with radioiodine 131 was negative and substitutional-suppressive therapy with levothyroxine was initiated. Complete multidisciplinary diagnostic evaluation for MALT lymphoma was performed with confirmation of PTL stage IE, thus no further therapy was conducted. Ten months after surgery, presented patient is without recurrence.

Conclusions
Optimal management of coexisting PTC and MALT lymphoma depends on stage of both diseases at the initial presentation. In patients with HT, attention should be focused on frequent concomitant PTCs and possible occurrence of lymphomas, thus total thyroidectomy represents a therapy of choice.

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EP1290
Nephrogenic syndrome of inappropriate antidiuresis secondary to an activating mutation in the arginine vasopressin receptor AVPR2

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Case history
A 38-year-old man was referred with a 12-month history of recurrent bouts of transient hyponatraemia (serum sodium ranging from 115 to 125 mmol/l). Citalopram, which he was taking for depression, was discontinued, but the episodes continued.

Initial investigations
Whilst symptomatic, and clinically euvoaemic, his biochemical profile was consistent with a syndrome of inappropriate antidiuresis (SIAD): sodium 124 mmol/l, potassium 4.5 mmol/l, glucose 6 mmol/l, urea 4.7 mmol/l, creatinine 76 μmol/l, serum osmolality 260 mOsm/kg, urine osmolality 652 mOsm/kg, and urine sodium 154 mmol/l. A contemporaneous anterior pituitary profile, including short Synacthen test, was normal, as were urinary porphobilinogen, head, chest, and abdominal CT were unremarkable.

Laboratory studies
A water load test was arranged: after 4 h he had excreted just 15% of a 20 ml/kg oral load (normal range 78–82%) and his serum sodium fell from a baseline of 134 mmol/l to a nadir of 125 mmol/l (serum osmolality 266 mOsm/kg and urine 808 mOsm/kg), consistent with inappropriate antidiuresis. Despite this, his AVP levels were profoundly low (0.4–0.9 pmol/l) throughout the test, indicating a nephrogenic syndrome of inappropriate antidiuresis. Sanger sequencing of AVPR2 revealed a missense mutation (X-linked) in a highly conserved arginine residue in the second intracellular loop (R137C). The mutant receptor exhibits constitutive activity when compared with its WT counterpart in transient transfection assays.

Discussion
Confirmed cases with activating mutations in AVPR2 causing nephrogenic SIAD are rare, with only sixteen cases reported worldwide since the syndrome was first described in 2005. However, this disorder may be underdiagnosed, based on historical reports of AVP levels in unexplained hyponatraemia. The ability to find a definitive cause in this case has provided validation to our patient, given a rational for preventative management with fluid restriction, and allows the potential for family screening.

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EP1291
Nephrotic syndrome due to membranous nephropathy as the cause of rising TSH levels or primary hypothyroidism as the cause of nephrotic syndrome? A case report

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We present a case of a 52-year-old man with a past medical history of primary hypothyroidism on treatment, presenting with elevated TSH levels, suggesting inadequate thyroxine (T4) replacement. The patient was managed with 200 μg of T4 for 14 years with no compliance issues. TSH levels failed to normalise despite increasing the dose of T4. In addition to elevated TSH levels the patient noted progressive leg swelling and associated shortness of breath over the preceding 12 months. Examination revealed bilateral pitting oedema up to the abdomen and elevated blood pressure (175/103 mmHg). Initial blood results demonstrated a low albumin of 21 g/l, down from a previous 44 g/l with urinalysis confirming marked proteinuria (+3) in addition to blood (+2). Subsequently, nephrotic syndrome was investigated as a probable cause. Twenty-four hour urinary protein was raised at 12.42 g (normal <0.15 g). A kidney biopsy was performed which demonstrated membranous glomerulonephritis. The nephrotic syndrome was
symptomatically managed on frusemide 40 mg b.d. and ramipril 10 mg o.m. The proteinuria improved with reduction of peripheral oedema and stabilization of TSH levels. There are numerous causes of elevated TSH levels in a primary hypothyroidism patient on \( T_2 \). One of the less common causes is nephrotic syndrome, characterized by oedema, hypoalbuminemia and proteinuria. Increased glomerular permeability results in loss of thyroxine-binding globulin (TBG) and free T3/T4. As a result, the pituitary–hypothalamic axis responded.

Increased glomerular permeability results in loss of thyroxine-binding globulin (TBG) and free T3/T4. As a result, the pituitary–hypothalamic axis responded.

It is important to recognise that many hormones are protein based, as are their carrier molecules calling for a closer analysis of symptoms on presentation of elevated TSH.

**EP1292**

Clinical case: gender identity disorder as an aetiology of hypothalamic amenorrhoea

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Hypothalamic amenorrhoea is a diagnosis of exclusion, frequent cause of which are medications or psychiatric disorders (bulimia/anorexia). Here we present a case, when its aetiology was gender identity disorder. A 18-year-old girl presented with absence of menses during last year. Menses began at the age of 14 and were regular till age of 16, when she moved to another city. She was seen by gynaeocologist because of amenorrhea, and evaluation was performed: FSH 4.6 mIU/ml (3.0–10.0), LH 7.2 mIU/ml (1.68–15.0), oestradiol 20 pg/ml (68–606), total testosterone 0.5 nmol/l (0.38–1.97), TSH 2 mU/l (0.4–4.0), prolactin 570 mU/l (109–557), and US, multifocal ovaries. ‘Ovarial hypofunction’ was established, and vitaminotherapy was prescribed without any effect. She appealed to different specialists, however, definitive diagnosis wasn’t established. At the age of 17, menses were recovered spontaneously and stopped again in 6 months. Patient had not taken OC, weight remained stable. Physical examination revealed BMI 19 kg/m², hirsute number 0, breast development Tanner 5. Hormonal test results were in reference range, hCG was negative. Talking with patient, our attention was drawn by her hysterical behaviour, because she told about herself as an asexual being. Thereby, she appealed to psychiatrist, and diagnosis of gender identity disorder was established. It was interesting to note that her menses recovered at that time, when she fell in love and felt as a woman. Taking into consideration absence of pregnancy, excluded endocrine causes of amenorrhoea, no history of OC, no excess or insufficient food intake, spontaneous menses recover during normal identity, there was established diagnosis of hypothalamic amenorrhoea, and psychiatric treatment was recommended. In case of amenorrhoea, body weight changes, and careful inspection are needed while suspicion of bulimia/anorexia. It is also needed to pay attention to patient’s speech, which may be a clue to diagnosis of gender identity disorder as a cause of hypothalamic amenorrhoea.

**EP1293**

Multiple endocrine neoplasia type 2A in a Turkish family presented with nonspecific symptoms

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Introduction

Multiple endocrine neoplasia type 2A (MEN2A) is a complex autosomal dominant inherited syndrome characterized by medullary thyroid carcinoma (MTC), pheochromocytoma, and primary parathyroid hyperplasia (PPH). In patients with only one or two clinical features, identification of a germline rearranged in transfection (RET) mutation or the identification of the clinical features of MEN2A in other first degree relatives is required to make the diagnosis. We present the case of a family with MEN2A syndrome, diagnosed with the complaint of abdominal pain.

Cases

Index case was the brother – OS – aged 28 years and was admitted to the hospital with the complaint of abdominal pain. There was no pathology in his medical history and physical examination. In radiologic examination; bilateral adrenal adenoma, multinodular goitre (MNG) and PPH was detected. Fine-needle aspiration cytology (FNAC) revealed MTC. And then operated for MTC, pheochromocytoma, and PPH. Genetic analysis showed RET gene mutation in 634codons. His father was died from myocardial infarction 5 years ago. Upon that all family members were investigated for MEN. Second case (brother, GS, aged 27 years), third case (sister, AK aged 32 years), and fourth case (sister, LK, aged 22 years) had also MNG in thyroid USG examination, PPH and FNAC revealed MTC. Operations also decided for them. Biochemical and hormonal parameters of cases are as shown in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Case 1, OS</th>
<th>Case 2, GS</th>
<th>Case 3, AK</th>
<th>Case 4, LK</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRA (mg/dl)</td>
<td>5.82</td>
<td>11</td>
<td>21.07</td>
</tr>
<tr>
<td>PAC (mg/dl)</td>
<td>0.37</td>
<td>0.78</td>
<td>4.46</td>
</tr>
<tr>
<td>Norepinephrine (urine)</td>
<td>1054</td>
<td>3401</td>
<td>1120</td>
</tr>
<tr>
<td>Metanephrine (urine)</td>
<td>3211</td>
<td>14527</td>
<td>1831</td>
</tr>
<tr>
<td>Cortisol (μg/dl)</td>
<td>15</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>TSH (mU/l)</td>
<td>2.2</td>
<td>11.8</td>
<td>2.86</td>
</tr>
<tr>
<td>DHEAS (μg/dl)</td>
<td>215</td>
<td>150</td>
<td>148</td>
</tr>
<tr>
<td>Calcitonin (pg/ml)</td>
<td>622</td>
<td>132</td>
<td>40</td>
</tr>
<tr>
<td>Parathormone (pg/ml)</td>
<td>145</td>
<td>91</td>
<td>87</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>11.5</td>
<td>11</td>
<td>10.3</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>4.2</td>
<td>4.3</td>
<td>4.3</td>
</tr>
<tr>
<td>Phosphor (mg/dl)</td>
<td>2.6</td>
<td>3.6</td>
<td>4.1</td>
</tr>
<tr>
<td>DST cortisol (μg/dl)</td>
<td>1.3</td>
<td>0.9</td>
<td>1.4</td>
</tr>
<tr>
<td>PR, plasma renin activity; PAC, plasma aldosterone concentration; DST, dexamethasone suppression test.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Discussion

MEN2A is the most prevalent form and presents with MTC in 95% of cases, bilateral pheochromocytoma in 50% of the cases and primary hyperparathyroidism in 25% of cases. Bilateral adrenal adenomas determined at a young age should be investigated interns of MEN syndrome. Also, in our index case bilateral adrenal adenomas were incidentally detected. In light of the association between certain familiar syndromes and patients diagnosed with pheochromocytoma, MEN2A syndrome at a young age should be screened with genetic testing for a RET mutation.

**EP1294**

Cervical paraganglioma ultrasonographically mimicking parathyroid adenoma: a case report

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Introduction

Paragangliomas are neuroendocrine tumors arising from extra-adrenal chromaffin cells. Paragangliomas of the head and neck frequently originate from the paraganglionic system including the carotid bifurcation, middle ear and the ganglion nodosum of the vagus nerve. However, of paragangliomas of the head and neck, only 1–3% secrete hormones and majority are non-functional. Here, we describe a case of non-functional paraganglioma confused with parathyroid adenoma ultrasonographically.
EP1296
Radioguided excision of occult metastatic lesion in thyroid carcinoma: a safe technique for previously operated neck in two patients
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Portuguese Institute of Oncology, Coimbra, Portugal.

Introduction
Intraoperative identification of neck lesions in patients who have undergone previous neck surgery is particularly difficult, because of operative scarring and distorted anatomy. Radioguided occult lesion localisation (ROLL) involves the preoperative intratumoral ultrasound-guided injection of a radioactive tracer. In the present study, we investigated the efficacy of roll in two patients with papillary thyroid cancer (PTC) who underwent previous neck exploration.

Material and methods
This study included two patients with recurrent/persistent PTC who have previously undergone operation. Patient 1: female, 65 years with PTC (T1bN1bM0) previously operated in 2010 with recurrence in the central neck (node with 9×7 mm). A fine-needle aspiration (FNA) cytology with FNA thyroglobulin (Tg) measurement was performed and confirmed the diagnosis of malignancy; patient 2: male, 50 years with PTC (T4aN1bM0) previously operated four times with three nodules in the central neck with 9, 7, and 6 mm. The largest node was submitted to FNA cytology confirming recurrence. In both patients 99mTC-labeled macroaggregated albumin was injected directly into each lesion under US guidance 90 min before surgery. Scintigraphy was performed 30 min after injection to visualize the focally increased uptake of radiotracer.

Intraoperative lesion detection was performed with gamma probe by identifying areas of maximum radioactivity.

Results
In patient 1 the lesion was identified and excised but in the patient 2 only two lesions were identified and excised. Histopathological examination confirmed recurrence of PTC in all of the nodules excised. In patient 1 serum Tg dropped from 15 to <2 ng/ml but in patient 2 Tg didn’t drop significantly and in the follow-up persisted a 7 mm nodule in the central neck.

Discussion
The Roll technique was efficient and safe in the perioperative identification of recurrent thyroid cancer in the central neck. This technique might help decrease the complications rates associated with reoperation.

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EP1297
Familial hypocalcemic hypercalcaemia: case report
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Introduction
Familial hypocalcemic hypercalcaemia (FHH) is a rare genetically heterogeneous disorder, with 3 variants described. An inactivating mutation in the calcium sensor receptor (CASR) gene causes the subtype 1, which represents 65% of the cases. It is characterised by hypercalcaemia and hypocalciuria with normal or elevated PTH. FHH is generally asymptomatic and treatment is not needed. Differential diagnosis with primary hyperparathyroidism (PHP) is crucial and based on calcium-creatinine clearance ratio (CCCR), which, when under 0.02 points to the diagnosis of FHH. Genetic test is necessary for confirmation.

Case report
An asymptomatic 16-year-old girl was referred to Endocrinology Department due to hypercalcaemia. Family history of several malignancies was present. Her mother died at 39 years old from hepatocellular carcinoma, her maternal-aunt at 18 from ovarian carcinoma. Laboratory work-up: Ca 11.5 mg/dl (8.8–10.4); P 3.1 mg/dl (2.5–4.5); Ca(u) 92 μg/dl (80–100); PTH 32 pg/ml (10–70); creatinine 0.7 mg/dl; and CCCR 0.007. DNA sequence analysis of CASR gene identified a frameshift mutation in exon 7, (c.1945delG), in heterozygosity, not previously described. Her father and half-brother had normal Ca and PTH levels. Some months later, patient maternal grandmother was observed for multinodular goitre and laboratory work-up
Graves' orbitopathy coursing with hypothyroidism: a case-report

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Introduction
Graves' orbitopathy is usually associated with Graves' Disease, which is typically characterized by hyperthyroidism and goiter. However, in rare situations, Graves' disease can also present with hypothyroidism and orbitopathy.

Case report
Male, 38 years old, followed by his ophthalmologist for thyroid orbitopathy (exophthalmos right > left and conjunctival hyperaemia since 1 year ago) associated with asthma, tiredness and weight gain. He was referred to endocrinology consultation because he presented TSH elevated (62.75 µU/mL, reference values (RV): 0.35–4.94) with normal FT3, 0.70 ng/dL (RV: 0.70–1.48) and normal FT4, 2.95 pg/mL (RV 1.71–3.71) and high levels of anti-thyroid and TSH receptor autoantibodies (TRAbs) (3.2 U/L (RV: 0–1.8)). Thyroid ultrasonography showed a gland with normal dimensions, heterogeneous and pseudo-nodular texture, suggesting thyroiditis. The patient denied any previous treatment. He started therapy with levothyroxine and the dose was increased as needed. It was accompanied by improvement of hypothyroid symptoms. Six months later, he had normal TSH and TRAb’s (3.9 U/L (RV: 0–1.8)). A year after starting therapy, symptoms reappeared and analytically he presented again with hypothyroidism (TSH = 14.71; FT3 and FT4) and TRAb’s levels > 40.0 U/L.

Discussion
It has been described in literature different types of TRAbs, which are capable of inducing two distinct clinical syndromes: thyroid-stimulating autoantibodies and TSH-blocking autoantibodies. In this patient with Graves' orbitopathy, a predominance of blocking type TRAbs vs stimulatory type may be a possible explanation for the presence of hypothyroidism. Although, we can't exclude the possible contribution, at least at some degree, from the gland's destruction (suggested by high titres of anti-peroxidase/anti-thyroglobulin autoantibodies and the findings suggestive of thyroiditis in ultrasound). Thus, the determination of TRAbs subtype is of particular interest in these less common forms of presentation of thyroid autoimmune pathology.

DOI: 10.1530/endoabs.37.EP1299

Graves' orbitopathy with thyroid hormone therapy

Case report
A 40-year-old female patient, presented to our hospital with symptoms of thyrotoxicosis. On physical examination heart rate was 120 b.p.m., blood pressure of 130/90 mmHg, with a nontender thyroid gland, with murmurs on auscultation, of 130/90 mmHg, with a nontender thyroid gland, with murmurs on auscultation, of 130/90 mmHg, with a nontender thyroid gland, with murmurs on auscultation, of 130/90 mmHg, with a nontender thyroid gland, with murmurs on auscultation, of 130/90 mmHg, with a nontender thyroid gland, with murmurs on auscultation, of 130/90 mmHg, with a nontender thyroid gland, with murmurs on auscultation, of 130/90 mmHg, with a nontender thyroid gland, with murmurs on auscultation, with moderately elevated antithyroid antibodies. The hypothyroidism was still under discussion. On the other hand in neurology are described new pathologic entities, which can occurred also by endocrine patients.

Methods
Recently the Hashimoto encephalopathy is more frequent recognised and successfully treated. The diagnosis criteria and treatment options however are still under discussion. On the other hand in neurology are described new pathologic entities, which can occurred also by endocrine patients.

Results
We have serious doubts regarding the diagnosis. The clinics including a strong dependence on steroids would speak rather for CLIPPERS syndrome? It is a link between Hashimoto encephalopathy and CLIPPERS syndrome?

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Introduction
Differents forms of brain damages in endocrine disease are relatively common. Recently the Hashimoto encephalopathy is more frequent recognised and successfully treated. The diagnosis criteria and treatment options however are still under discussion. On the other hand in neurology are described new pathologic entities, which can occurred also by endocrine patients.

Case
In September 2009 by the 66 years old women with type 2 diabetes and metabolic syndrome was diagnosed hypothyroidism in course of autoimmune thyroiditis with moderately elevated antithyroid antibodies. The hypothyroidism was successfully treated with levothyroxine, but in December 2012 patient was admitted with cognitive decline and impaired mobility. In CT brain metastases are described but the primary focus are not found. In brain biopsy was found inflammatory infiltration from the T and B lymphocytes and macrophages, reactive glosis and loss of myelin. After steroids, initially as pulses of 1 g methylprednisolone and then oral prednisone (60 mg with subsequent reduction) clinical status was improved and in MRI we observed brain damage regresses until almost complete in November 2013. In May 2014 when attempting to further reduce the dose of steroids visual loss occurred on the right eye. The vision returned after pulses of methylprednisolone, which we have repeated in subsequent months. The patient is currently in a stable condition on oral 25 mg prednisone. Diabetes and hypothyroidism are treated effectively. She sees and moves quite well, although she had a depressed mood.

Discussion
We have serious doubts regarding the diagnosis. The clinics including a strong dependence on steroids would speak rather for CLIPPERS syndrome, but we cannot exclude pathology associated with thyroiditis, despite the relatively low titre of antithyroid antibodies. Therefore we would like to introduce our problem, to the European Endocrinologists in hope for comments and advice.

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Incidental thyroid cancer in a subcentimetre nodule with benign ultrasound criteria in a patient with Graves’ disease

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Department of Endocrinology, University Hospital Center ‘Mother Theresa’, Tirana, Albania.

Introduction
A thyroid nodule discovered in a patient with Graves’ disease (GD) should be evaluated and managed according to guidelines. A subcentimetre incidental thyroid cancer founded in a patients with GD, without high-risk history, without suspicious sonographic (US) features has not been reported yet.

Clinical case
A 40-year-old female patient, presented to our hospital with symptoms of thyrotoxicosis. On physical examination heart rate was 120 b.p.m., blood pressure of 130/90 mmHg, with a nontender thyroid gland, with murmurs on auscultation, of 130/90 mmHg, with a nontender thyroid gland, with murmurs on auscultation, of 130/90 mmHg, with a nontender thyroid gland, with murmurs on auscultation, of 130/90 mmHg, with a nontender thyroid gland, with murmurs on auscultation, of 130/90 mmHg, with a nontender thyroid gland, with murmurs on auscultation, of 130/90 mmHg, with a nontender thyroid gland, with murmurs on auscultation, of 130/90 mmHg, with a nontender thyroid gland, with murmurs on auscultation, of 130/90 mmHg, with a nontender thyroid gland, with murmurs on auscultation, of 130/90 mmHg, with a nontender thyroid gland, with murmurs on auscultation, of 130/90 mmHg, with a nontender thyroid gland, with murmurs on auscultation, with moderately elevated antithyroid antibodies. The hypothyroidism was still under discussion. On the other hand in neurology are described new pathologic entities, which can occurred also by endocrine patients.

Methods
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Results
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DOI: 10.1530/endoabs.37.EP1300

17th European Congress of Endocrinology 2015

Endocrine Abstracts (2015) Vol 37
EP1301
Late onset of a rare autoimmune association: coeliac disease and Hashimoto's thyroiditis: hormonal and metabolic implications
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Introduction
Several autoimmune determinations have been reported in association with autoimmune thyroiditis (AIT). While the classical correlations with other endocrine or general autoimmune diseases like pernicious anemia or vitiligo are frequent and well defined, there are fewer data on other rarer associations, as with celiac disease (CD). In the absence of typical clinical symptoms this association may be overlooked, as in the case we present.

Case presentation
DM, 64 years old female patient, with three recent episodes of persistent diarrhea and weight loss, having negative bacteriologic and imagistic investigations (gastric endoscopy with antral biopsy, colonoscopy, and abdominal CT), was oriented to the Endocrine Department for hypothyroidism associated with severe dyslektrelasia. On admission she presented asthenia, hypoanabolic syndrome (BMI 17.5 kg/m2) and inferior limb edema. Biological data confirmed autoimmune thyroiditis with hypothyroidism (TSH = 27 µU/mL, FT3 = 0.7 ng/dl, ATPO > 1000 UI/mL, and ATG > 3000 UI/mL), inflammatory syndrome, severe vitamin D deficiency (< 3 ng/ml), and severe metabolic disturbances (hypoalbuminemia, hypokalemia, hypotremia, hypocalcemia, and acidosis). Markers for digestive neoplasia and NET were negative. Other investigations revealed osteoporosis and profound venous thrombosis with decreased tolerance to cumarinic anticoagulants (INR 7.32) which imposed heparinotherapy. Coeliac disease was suspected, sustained by positive antigliadin antibodies. Patient refused duodenal biopsy. Substitutive l-T3 treatment, vitamin D supplementation and gluten-free diet was started, with rapid and persistent improvement of the general status and biological data.

Conclusion
Undiagnosed CD associated with AIT may determine severe metabolic disturbances due to the vicious circle of malabsorption. Low l-T3 absorption impose attentive substitution dosage. Most of guides do not recommend systematic search of CD in AIT however, since, as in our patient, CD may be paucisymptomatic and/or with late manifestation, we believe that it may be useful to search it, if not in all AIT patients at least in those with metabolic disturbances.

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EP1302
Malignant ectopic thyroid tissue with distant metastasis: a case report
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Introduction
Ectopic thyroid tissue is the most common form of thyroid dysgenesis. But primary malignant transformation in ectopic thyroid tissue is quite a rare entity, with follicular malignancy being the dominant form at ectopic sites. Very infrequently, malignant ectopic thyroid tissue can present with metastasis to lymph nodes. But we report a case of malignant ectopic thyroid tissue over manubrium sterni with distant metastasis.

Case presentation
A 42-year-old Pakistani female presented with gradually increasing swelling on anterior aspect of manubrium sterni for last 6 months. She had no goitre and was clinically and biochemically euthyroid. Rest of systemic exam was also unremarkable. CT chest showed a circumscribed soft tissue density mass arising from sternum, measuring 3.9×3.9 cm, causing erosions of anterior, right lateral and posterior walls of sternum. Trucut biopsy of the sternal mass proved it to be thyroid tissue with follicular differentiation and occasional mitotic figures. Multiple nodules were also noted in thyroid gland in US neck. She underwent total thyroidectomy and excision of ectopic thyroid tissue over manubrium sterni. Extensive histopathological examination of primary thyroid gland showed benign nodules with hyperplasia with no evidence of malignancy. Ectopic thyroid tissue showed minimal invasive follicular thyroid carcinoma with tumor size of 3.2×2.3 cm. Her postoperative 21-day biochemical profile showed TSH 22.345 µIU/ml (0.4–4.2), serum thyroglobulin 88.3 ng/ml, and anti-TG antibodies < 20.0 IU/ml. Based on the histopathological diagnosis, she went through 30 mCi RAI-131 ablation. The post-ablative whole body scan showed good uptake of ablative dose over thyroid bed and evidence of multiple well-defined rounded areas of abnormally increased tracer accumulation over mid and lower dorsal spine, lumbar region and right iliac bone, representing bone metastasis. It was followed by MRI spine which showed foci of metastatic deposits in T1–T3 and L2 vertebral bodies and abnormal signals showing post-contrast enhancement in superior medastinum with invasion of medial ends of both clavicles, more marked on right side. So patient was found to have malignant ectopic thyroid tissue with distant bone metastasis.

Conclusion
We describe the first case of its kind having malignant ectopic thyroid with metastasis to spine and ilium. Such cases may impose difficulties in their treatment decisions.

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EP1303
Medullary thyroid carcinoma in multiple endocrine neoplasia 2A: a therapeutic challenge
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Introduction
Medullary thyroid carcinoma (MTC) occurs in a hereditary pattern in 25% of cases. Virtually all patients with multiple endocrine neoplasia 2A (MEN2A) develop MTC. MTC aggressiveness and natural history varies according to the RET mutation. Prophylactic thyroidectomy may cure and/or prevent metastatic disease in most cases.

Case report
A 27-year-old man with past history of colostomy at 5 months of age for Hirschsprung disease and total thyroidectomy at 14 years of age old for the genetic diagnosis of MEN2A (C620R RET). Patient’s underwent genetic study when his mother was diagnosed with MTC and a germline mutation in RET gene (C620R) was identified. Patient’s post-operative histological diagnosis revealed two MTC foci of 1 and 0.3 cm. Patient was lost to follow-up at the age of 16. In the last year he reported low back pain radiated to right thigh. MRI showed a 9×5×8 cm mass in the right iliac bone and lesion biopsy was compatible with MTC metastasis. 68Ga-DotaNoc PET showed uptake in the thyroid area, left para-pharyngeal region, high density of somatostatin receptors in the left cervical region and right iliac bone. Biochemical analysis revealed thyroglobulin of <0.2 ng/mL (1.6–6.0), calcitomin of 60.428 pg/ml (<10), and CEA of 1.947 ng/ml (<5.4). Patient underwent bilateral cervical lymph node dissection and subtotal resection of iliac metastasis. Histological examination confirmed MTC metastasis. Patient underwent a cycle of 200 mCi of 177Lu-DotaTate, though low radionuclide uptake motivated its withdrawal. Patient showed increased uptake of 177Lu-MIBG and treatment with 111In-MIBG was started (154 mCi).

Conclusion
CMT is the first manifestation of MEN2A. As shown in this case the age of prophyllactic thyroidectomy is of decisive importance to the prognosis. Tumour somatostatin receptors heterogeneity may be responsible for different responses to radionuclides. The treatment of metastatic disease is challenging due to the poor response to systemic therapy and/or radiotherapy.

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EP1304
Coexistent medullary and papillary thyroid carcinomas
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Papillary thyroid cancer (PTC) is the most frequent thyroid tumour. Medullary thyroid cancer (MTC) however, is very rare. We report a case of coexistent

Endocrine Abstracts (2015) Vol 37
Conversion of autoimmune hypothyroidism to hyperthyroidism with thyroid eye disease

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We report the case of a 41-year-old lady who developed severe thyroid eye disease on a background of long standing hypothyroidism. She had been diagnosed with autoimmune hypothyroidism 15 years previously with positive TPO antibodies. She had been successfully maintained on levothyroxine replacement since then. She presented with a four year history of progressive eye swelling, gritty eyes and diplopia. On examination she was found to have active thyroid eye disease with restriction of extra-ocular movement, proptosis and diplopia. In addition her thyroid function tests showed suppressed TSH indicating probable over replacement with thyroid hormone. Her levothyroxine dose was weaned and eventually discontinued. She proceeded to have a course of steroids with some reduction in her visual symptoms. Unfortunately, she developed significant symptoms of thyrotoxicosis off thyroid replacement. Thyroid uptake scan showed generally increased uptake in the right lobe with no evidence of a nodule on ultrasound. TSH receptor antibodies at this time were strongly positive. Unfortunately her eye disease relapsed and she required orbital decompression surgery to which she had a good functional and cosmetic response.

Commentary

This case report highlights the importance of correct dose adjustment on patients under levothyroxine replacement therapy and stresses that TSH should be determined in patients presenting with acute coronary syndrome and typical finding of TC.

DOI: 10.1530/endoabs.37.EP1307
hypothyroidism to hyperthyroidism in a patient rather than attributing the biochemical abnormality solely to over replacement with thyroid hormone.

**EP1308**  
Pulmonary neuroendocrine tumour presenting with thyroid gland metastasis: a case report  
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**Introduction**  
Neuroendocrine tumours (NET) represent ~20% of all primary neoplasms of the lung. Histologic confirmation is important for treatment and prognosis determination. NET are classified according to four subtypes in the lung: typical carcinoid tumour (TC), atypical carcinoid tumour (AC), small cell carcinoma (SCC), and large cell neuroendocrine carcinoma (LCNEC). TC is low-grade, AC is intermediate-grade, and SCC and LCNEC are high-grade malignancies.

**Case report**  
A 57-year-old woman, affected by a cervical anterior tumour and a proliferative tissue below the glottis was referred to our Endocrinology Department from ENT service for a second opinion. An ultrasound scan of the neck showed a polynodular goitre with bilaterally lymph nodes enlargement with suspicious malignancy characteristics. She had undergone surgery for the cervical anterior mass and for the laryngeal biopsy. Histopathological examination results were consistent with a SCC; neoplastic cells showed immunoreactivity to synaptophysin, neuron specific enolase, and chromogranin. The serum levels of serotonin, chromogranin A, calcitonin, carcinoembryonic antigen, ACTH, FTH, TSH, and FT4 were normal. Fine-needle aspiration biopsy of her left thyroid lobe nodule was performed and the cytopathological exam was compatible with a neuroendocrine tumour metastasis. Thoracic and abdominal computed tomography was normal at that moment. Chest CT revealed the primary pulmonary tumour at 6 months after presentation. The therapeutic option for advanced or metastatic NETs is mainly palliation of symptoms; options need to be individualised and, therefore, rely on the knowledge of multidisciplinary teams.

**EP1309**  
Graves’ disease and pregnancy  
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**Introduction**  
Pregnancy for women with Graves’ disease is at risk for the mother and the newborn. In fact neonatal hyperthyroidism is uncommon, often transient in the context of maternal Graves’ disease (1% of children). Immediate treatment is essential for a good prognosis, prenatal treatment improves foetal and neonatal development.

**Case report**  
We report the case of a patient, known for Graves’ disease since 2006, treated initially with carbimazole for 18 months. She was in remission for 2 years, but in December 2013 as she relapsed, she was treated by radio-iodine (one month before conception). She gave birth to a premature 31 SA, in 21 August 2014 with subclinical hyperthyroidism (TSH: 0.07 Ul/ml and FT4: 7.09 pg/ml). After 15 days the new born present an overt hyperthyroidism (TSH: 0.01 Ul/ml and FT4: 23.5 pg/ml) with TSI: 6.89 UI. The baby receives carbimazole for 2 months and became euthyroid.

**Conclusion**  
Neonatal hyperthyroidism should be screened in all newborn from mother with Graves’ disease treated by radical treatment (radio-iodine or thyroidectomy) because TSI freely cross the placental barrier and thus stimulate the thyroid of the newborn. Prognosis of neonatal hyperthyroidism mediated by anti maternal body is quite good as they disappear in 4–12 weeks after birth.

**EP1310**  
The Ehlers-Danlos syndrome and metastatic medullary thyroid carcinoma: a case report  
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**Introduction**  
The Ehlers-Danlos syndrome, classic type is a connective tissue disorder, characterized by skin hyperextensibility, abnormal wound healing, and joint hypermobility, due to COL5A1 or COL5A2 genes mutations. Multiple endocrine neoplasia, type 2A (MEN2A) is a syndrome defined by medullary carcinoma, pheochromocytoma, hyperparathyroidism, and occasionally cutaneous lichen amyloidoses, because of mutations in RET proto-oncogene. COL5A1 and RET genes mutations are linked to conditions affecting the human integumentary system.

**Case report**  
A 18-year-old Caucasian female was consulted by endocrinologist in February 2014. Her psychomotor development was normal. Since childhood she was very flexible. At age 12 she had hip luxation and underwent internal fixation with screws. Deformities of pelvis and lumbar spine, knee valgus deformity occurred. At 15 years juvenile epiphysiolysis was diagnosed. She underwent left knee osteosynthesis followed by peroneal and tibial nerves damage. In 2012 small thyroid nodule, subclinical hypothyroid was diagnosed; 25 mg of levothyroxine were prescribed. In 2014 medullary carcinoma (size 0.4 mm) was diagnosed. Thyroidectomy and neck lymphnodectomy was performed. She received radiotherapy course. 2.5 weeks after surgery calcitonin level was 1557.2 ng/l (0.5–7.8). She has been taking levothyroxine 125 mg/day. Her mother has MEN2A and underwent surgery for parathyroid adenoma. Father has multinodular goitre. On examination: height 184 cm, long face, long palms and fingers, joints’ hypermobility, scoliosis, widened atrophic scars, atrophic striae at the back, hyperelasticity of face and elbows skin, pizeogenic papules. Abdominal ultrasound and CT: no pathological changes. Left shoulder CT: sclerotic proximal growth line of left humerus. Body CT: multiple lymphnodes, lungs, pelvis bones, and vertebral metastases. Bone scan: active head, humerus, pelvis focuses. Genetics’, Ehlers-Danlos syndrome; RET gene mutation at 13th egzone (1791F mutation), causing MEN2A syndrome.

**Conclusions**  
If complicated growth and atypical phenotype is obvious, genetics’ consultation is desirable. Coexistent thyroid pathology might be inherited too.

**EP1311**  
Takotsubo cardiomyopathy in a young woman with severe adrenal insufficiency and hypothyroidism  
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**Introduction**  
Acute cardiac insufficiency induced by stress (Takotsubo cardiomyopathy (TTC)) is a reversible cardiomyopathy induced by severe emotional stress or severe clinical conditions. It is characterised by transient left ventricular systolic dysfunction and electrocardiographic changes. This cardiomyopathy has been described in some severe neurological conditions and in patients with pheochromocytoma. To date, some cases of this cardiomyopathy have been described in patients with hypopituitarism due to isolated secondary adrenal insufficiency or in a patient with both hypothyroidism and adrenal insufficiency. TTC has been known to be more prevalent in women (the role of sex and hormones is not yet well defined).

**Case report**  
We present a case of a 43-year-old woman with hypopituitarism, probably due to autoimmune hypophysitis with secondary hypothyroidism, secondary adrenal hypo
Insufficiency, and hypogonadism as well as with primary hypothyroidism due to Hashimoto’s thyroiditis. The patient was treated for primary hypothyroidism, but her general condition suggested adrenal insufficiency. On admission, her plasma cortisol was 0 μg/dL, so she was treated immediately with hydrocortisone. As a routine examination, echocardiography was performed revealing ampulla cardiomyopathy. Electrocardiography showed T wave inversion in almost all leads. Two weeks after treatment with hydrocortisone and thyroxine, an echocardiographic examination showed recovered left ventricular wall motion and improvement in the ejection fraction and electrocardiography was normal. This is, to our knowledge, the first report of TTC due to hypothyroidism and adrenal insufficiency with no hypotension, no evident hypoglycaemia and no evident catecholamine overproduction.

Conclusions
Adrenocortical failure is considered to be one of the triggering factors for ampulla cardiomyopathy. All patients with severe adrenal insufficiency should be screened for cardiomyopathy and first-line treatment in these cases consists of proper steroid substitution and careful monitoring of cardiac function.

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EP1312
A rare association: primary hyperparathyroidism and thyroid papillary carcinoma: case report

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Introduction
Although, the relationship between pathological process of the parathyroid and thyroid is common, concurrence of primary hyperparathyroidism (pHPT) and papillary thyroid carcinoma (PTC) is extremely rare, probably because, unlike with medullary thyroid cancer, they have not a common embryologic origin. We present a case with this uncommon association.

Case report
A 67-year-old woman with multinodular goitre was addressed in endocrinology for persistent hypercalcaemia 11.24 mg/dl and hypophosphataemia 2.4 mg/dl. High PTH value (119 pg/ml (normal range 10–69 pg/ml) confirmed primary hyperparathyroidism. The neck ultrasound revealed a potential 0.4 ml parathyroid adenoma at the superior pole of the right thyroid lobe and a 6 ml nodular conglomerate with central necrosis in the left thyroid lobe. The 99mTc-sestamibi parathyroid scintigraphy revealed an area with increased uptake in the projection of the right upper parathyroid gland and a focused uptake at the left lower parathyroid gland. However, 99mTc-sestamibi thyroid scintigraphy did not reveal any uptake in the left upper parathyroid gland.

Hyperparathyroidism was cured, with normal PTH and phosphocalcic activity and her thyroid biopsy resulted as consistent with subacute thyroiditis. ESR, CRP, anti-TG, and anti-TPO were much more higher. It was learnt that she had been vaccinated for influenza 3 weeks ago and began to suffer from gripal symptoms at the third day and pain and swelling of thyroid at the second week of vaccination. Her thyroid scintigraphy showed heterogeneous and lower activity and her thyroid biopsy resulted as consistent with subacute thyroiditis. So the patient was diagnosed as subacute thyroiditis and subacute thyroiditis was began besides raising levothyroxine dose to 100 μg/day. Methyl prednisolone of 40 mg/day was added because there was no symptomatic improvement at the third day. The symptoms regressed after steroid in three days and recovered totally at the end of the first week. Steroid was stopped by gradually declining at the third week.

Discussion
Influenza like symptoms is known to develop after vaccination. This case is showing a rare condition due to vaccination to cause a subacute thyroiditis just like the virus can make.

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EP1313
Fainting matters: a case of an autoimmune polyglandular syndrome with an atypical involvement of the parathyroid gland

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Introduction
The autoimmune polyglandular syndrome (APS) is characterised by the coexistence of at least two glandular autoimmune mediated diseases. We report a combination of an autoimmune thyroid disease, Addison’s disease and an atypical involvement of the parathyroid gland.

Case report
A 73-year-old white woman was admitted to our clinic for evaluation due to recurrent syncopes during last 3 years, along with vertigo, cold sweats, and general fatigue, associated with prolonged standing. Three months ago she was diagnosed with chronic autoimmune thyroiditis and primary hypothyroidism, as well as a parathyroid gland adenoma. Head CT scan revealed basal ganglia calcinosis. The patient had lost 15 kg within the past year, during investigation orthostatic hypotension was detected, no skin colour changes. Biochemical tests revealed low aldosterone, renin, calcium, free T3 and mildly elevated creatinine serum levels. TSH was elevated, ACTH was high normal. She had low cortisol in 24 h urine and also in serum after insulin stress test. PTH level was normal, but coexisting hypocalcaemia and parathyroid gland adenoma must be taken into consideration. Antibody screen (ANA, thyroid peroxidase, and transglutaminase) was negative. No substantial changes in other tests. No data on diabetes mellitus or malignancy was found. Diagnosis of primary adrenal insufficiency with glucocorticoid and mineralocorticoid deficiency, chronic autoimmune thyroiditis with primary hypothyroidism, hypocalcaemia, calcinosis of basal ganglia (possible Fahr’s syndrome), parathyroid gland adenoma, secondary osteoporosis due to malabsorption, chronic kidney disease was made. Based on these findings we suggest the final diagnosis of type 2 autoimmune polyglandular syndrome.

Treatment was continued with l-thyroxine and oral calcium, started with alphacalcidol, hydrocortisone, fludrocortisone. A substantial improvement of symptoms was seen in a control visit after 3 months.

Conclusion
We would like to stress the importance of investigation for autoimmune glandular diseases and electrolyte level in case of unexplained syncope.

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EP1315
Testicular pain as an initial complaint in patient with classic form of Klinefelter’s syndrome: a case report
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Background
In spite of being the most frequent genetic form of male hypogonadism, Klinefelter’s syndrome is not so rarely undiagnosed until adulthood. As the severity of manifestations in Klinefelter’s syndrome is proportional to the number of additional X chromosomes, they seem less severe and apparent in its classic form, with a 47,XXY karyotype than in cases of this syndrome with mosaicism and other variants.

Case report
A 25-year-old male was referred for endocrine evaluation by urologist because of the chronic testicular pain preventing effective testosterone replacement of already proven hypogonadism. The physical examination revealed normal height, long limbs, muscular weakness, and reduced or completely absent hair in the androgen-dependent regions. There are clinical signs of testicular dysgenesis. Hormone measurements were as follows: ACTH, 37.74 pg/ml; cortisol, 505.9 nmol/l; TSH, 1.81 μIU/ml; FSH, 5.39 mIU/ml; free testosterone, 3.0 pg/ml; PRL, 519.9 mIU/l; and vitamin D, 21.25 ng/ml. MRI demonstrated a profound arachnoid recessus hustling the FSH, 53.39 mIU/ml; free testosterone, 5.0 pg/ml; PRL, 519.9 mIU/l; and vitamin

Conclusions
The case presented demonstrates a classical form of the Klinefelter’s syndrome with not so classical presentation of testicular pain which halted the correction of proven androgen deficiency. Coexistent empty sella with hyperprolactinaemia demand further periodical reassessment.

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EP1316
Ectopic ACTH syndrome: diagnostic and therapeutic challenge
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Introduction
Rapid deterioration of health condition in patient with diagnosed neoplastic disease, especially metastatic one, requires consideration of cancer progression. However other rare severe complications can occur. In 0.6–0.7% patients with medullary thyroid cancer (MTC) the ectopic ACTH syndrome (EAS) is observed. Hereby, we present a case EAS in patient suffered from MTC.

Case report
A 37-year-old man was admitted to the Department of Internal Medicine in serious clinical condition with general fatigue and chest pain. Myocardial infarction has been excluded. Patient’s past medical history was remarkable for MTC with numerous reoperations. Routine laboratory test showed de novo diabetes mellitus. Calcitonin serum level was 4995.3 pg/ml (n: 0–10 pg/ml). Additional tests revealed severe hypercortisolaemia (cortisol level 2100 nmol/l; T4, 15.15 pmol/l; LH, 31.78 mIU/ml; FSH, 53.39 mIU/ml; free testosterone, 3.0 pg/ml; PRL, 519.9 mIU/l; and vitamin D, 21.25 ng/ml. MRI demonstrated a profound arachnoid recessus hustling the pituitary toward the dorsum of the sella turcica. Densitometry showed osteopenia with the L1-L4 T-score of −2.7 and the hip T-score of −2.1. Assessment of the karyotype point out to the classic, 47,XXY form of Klinefelter’s syndrome and testosterone replacement was initiated with the close follow-up of its effects. 

Conclusions
The EAS is a rare condition in patients with MTC, but our patient’s history should serve as a warning to actively seek of EAS in case of metastatic disease, especially in rapid health deterioration.

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EP1317
Stress cardiomyopathy following radioactive iodine therapy: a case report
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A 55-year-old female presented to the Endocrine Clinic with Graves’ disease which was treated with carbimazole for 18 months. Her initial symptoms were facial sweating and dry lips on background of a multinodular goitre confirmed on thyroid ultrasound. TSH was <0.01 mIU/l, free T4 was 42.2, and free T3 18 pmol/l. Thyrotoxicosis recurred in an attempt to taper down the dose of carbimazole and a decision was made to proceed with radioactive iodine treatment. Four days after radioiodine administration, our patient presented to the Emergency Department with chest tightness and dyspnoea. TSH was undetectable and free T4 was 7.7 pmol/l. ECG was consistent with sinus tachycardia and borderline ST elevation in II/III leads. Troponin was elevated at 438 ng/l. Our patient was transferred to the local cardiothoracic center, where echocardiography revealed left ventricular ejection fraction of 30–35%. Coronary angiography showed no obstructive coronary disease. This is a case of stress cardiomyopathy which developed in the context of radiation thyroiditis. Complete recovery was achieved after treatment with propylthiouracil, ramipril, carvedilol, and a course of steroids. Six weeks later left ventricular function was noted to be normal on echocardiography and hypothryoidism was evident on thyroid function testing. This the second case of stress cardiomyopathy following radioactive iodine therapy reported in the literature, to the best of our knowledge. Left ventricular dysfunction is reversible in stress cardiomyopathy although patients can present quite urgently. High index of suspicion along with early thyroid testing may lead to successful treatment without unnecessary diagnostic investigations.

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EP1318
Is thymectomy a solution for myasthenia gravis associated with autoimmune thyroid diseases?
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Myasthenia gravis (MG) and autoimmune thyroid diseases (AITD) may coexist and influence one another clinical expression. The opportunity of thymectomy in this association is controversial, since not all the studies have proven its efficacy. We report eight patients (one man and seven women) diagnosed with AITD (Graves’ disease (GD) – five cases, Hashimoto’s thyroiditis (HT) – three cases) and MG. The AITD diagnosis preceded (two cases), followed (three cases) or occurred simultaneously (three cases) with MG. In most cases thyroid disease had a good evolution with medical treatment. Four cases underwent thyroidectomy; one for intolerance to antithyroid drugs, two severe relapse of GD, and one for large nodular goitre with compression symptoms. All patients had imagistic investigation of thymus area: CT, scintigraphy with 99Tc-tetrofosmin. Treatment was started with anticholinesterase drugs (ACh). Myasthenia was performed in six cases either for tumoural aspect on imagery or inefficacy of ACh. Surgery was performed, on demand, in one case with normal imagery and stable evolution. Thymectomy in this particular case did not modify the evolution. Three cases with evolution of MG for <1 year, had an improvement of the myasthenia after thymectomy. One of them, the man, who associated three autoimmune diseases, had also an improvement of the HT. One case, with a 4 years evolution of MG and HT, had no improvement after thymus resection. Last case had an unfortunate evolution, with postsurgical death. The two cases, not operated, had a good evolution of AITD followed by an amelioration of the MG symptoms. The association of MG and AITD may influence one-another evolution. Generally, the amelioration of the thyroid dysfunction induces an improvement of MG. Thymectomy may improve the evolution of MG if performed in the first year of diagnostic. Longer evolution leads to irreversible alterations; therefore the myasthenic symptoms cannot be improved.

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Prolactinomas and Leydig cells tumors are possible causes of gynecomastia

Introduction
Gestational diabetes insipidus (GDI) is a rare endocrinopathy whose incidence is around four cases per 100,000 pregnancies. It is a potentially life threatening state.

We present a case of a 39 year old with GDI.

Case report
A previously healthy 39-year-old woman in her 37th week of gestation presented dry oral mucosa with polydipsia and polyuria of 8 1/2 for approximately 2 months. The prenatal course of the pregnancy was uncomplicated until 35 weeks. Medical history was an appendectomy and she had on treatment of female infertility with in vitro fertilisation. On admission, well general condition, blood pressure 105/60 mmHg and 75 beats/min and saturating 99% on ambient air. The physical and gynaecological examinations were unremarkable. Laboratory studies revealed: serum sodium of 140 mEq/L, potassium 4.3 mEq/L, chloride 108 mEq/L, glucose 79 mg/dl, creatinine 0.7 mg/dl, calcium 8.2 mEq/L, total protein 5.9 g/dl, FA 140 units/l, AST 584 units/l, and ALT 613 units/l. The serum osmolality was 294 mOsm/kg; and urine osmolality was inappropriately low. Other laboratory data were normal. Water deprivation test and treatment with DDAVP confirmed diagnosis. Twelve hours after admission, she had a female baby by spontaneous vaginal delivery with APGAR scores were 8, 10 at 5, and 10 min, respectively. Laboratory evaluation of the infant was normal. Post-delivery, polydipsia and polyuria were resolved. GDI was resolved after delivery.

Conclusions
The diagnosis of gestational DI is often not diagnosed because polyuria in pregnancy is generally considered normal. We should suspect in patients with typical symptoms or with risk factor because sometimes, GDI can be associated with serious pathology like fatty liver of pregnancy and pre-eclampsia that might lead to foetal demise.

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Hyperprolactinemia and Leydig cell tumor

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Introduction
Leydig cell tumors are the most common testicular sex cord stromal tumors. The most frequent clinical presentation is a testicular mass. However, they can present with endocrine manifestations, and gynecomastia is the most common presentation. Hyperprolactinemia can cause hypogonadotropic hypogonadism, and in males, is also a cause of gynecomastia.

Clinical case
A 24-years-old male was referred to our Endocrinology Department due to hyperprolactinemia and increasing bilateral breast volume with a year of evolution, without galactorrhea, libido changes or erectile dysfunction. He had irrelevant medical past history, without medication, smoking, alcohol or illicit drug use. On physical examination, bilateral painful gynecomastia, without palpable nodules, skin changes or nipple retraction or galactorrhea. Testes were present, with no palpable nodules. Laboratory exams revealed normal testosterone and FSH, slightly low LH (1.43 mIU/ml (1.5–9.3)), high estradiol (206.02 pmol/l (<146.1)), although normal in its first evaluation) and high prolactin levels (27.08/35.49/50.30 ng/ml (2.1–17.7)). TSH was normal and testicular tumour markers were normal. Breast ultrasound showed increased bilateral mammary glands, compatible with gynecomastia. The pituitary MRI showed an area of low uptake which could correspond to a microadenoma. He started bromocriptine 2.5 mg/day. In the scrotal ultrasound an isochogenic nodule with 12 mm in the right testicle was observed. He was referred to the urology consultation. Scrotal RM confirmed the nodule in the right testicle. He was submitted to right partial orchiectomy guided by ultrasound, and histological examination revealed a Leydig cell tumor. He was oriented to plastic surgery to bilateral mastectomy. After surgery, we stopped bromocriptine use and pituitary MRI was normal. Currently, he has normal prolactin levels.

Discussion
Prolactinomas and Leydig cells tumors are possible causes of gynecomastia and hyperprolactinemia (in the last case because of hyperprolactenemia) making it sometimes a challenge the evaluation of prolactin levels in this context.

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Can pericardial effusion be a manifestation of Graves’ disease? An unusual case

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Introduction
Graves’ disease (GD) is associated with a number of cardiovascular complications, including rhythm disturbances, mitral valve prolapse, pulmonary hypertension and heart failure. Pericardial effusion in the context of GD has only been reported in a small number of cases.

Case
A 59-year-old gentleman presented with a 3-day history of dyspnoea and pleuritic chest pain. He had a previous history of GD 8 months ago, pulmonary embolism (PE), asthma, hypertension, and obesity was established on warfarin, following a second episode of PE, 4 weeks prior to this clinical event. Clinical examination revealed tachypnoea, tachycardia, raised JVP and bibasal crackles. Echocardiography showed a 2.9 cm pericardial effusion, compromising the right ventricular filling. 10 days prior to this admission, a previously echocardiogram had shown a smaller size pericardial effusion. TTEs showed suppressed TSH, elevated free T3 at 34.7 pmol/l (reference range 9.2–21 pmol/l) and positive TSH receptor antibodies, compatible with relapsed GD. Other laboratory investigations showed acute kidney injury (eGFR 38 ml/min per 1.73 m2) and elevated INR at 17.2, which was pharmacologically reversed. Interestingly, 10 days prior to admission the patient had normal renal function. Analysis of the pericardial fluid showed inflammatory cells. Microbiology and cytology investigations were unremarkable. A full body CT scan did not show evidence of neoplastic process. The patient was stabilised following pericardiocentesis and was commenced on Carbmazole 40 mg daily.

Conclusions
This is an unusual presentation of GD. The patient was investigated extensively, but no alternative cause for pericardial effusion was found. The presence of inflammatory cells in the fluid, suggests an inflammatory pericarditis. GD could have also been implicated in the pathogenesis of the patient’s recent PE, given the thrombogenic tendency that hyperthyroidism is associated with. We therefore recommend that TTEs should be undertaken in patients presenting with unexplained pericardial effusion and equally patients with GD presenting with dyspnoea should undergo echocardiography.

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Concurrent hyperthyroidism and thyroid cancer – case presentations

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Introduction
The coexistence of hyperthyroidism and thyroid cancer is rare (below 2% of cases with hyperthyroidism). If this association predisposes to larger, multifocal or more aggressive cancer (especially in Graves’ disease) is a matter of debate. We describe the clinical and histopathological aspects and evolution in two patients with hyperthyroidism and thyroid cancer.

Patient 1. A 42-year-old woman, was diagnosed in 2008 with Graves’ disease (overt hyperthyroidism, mild exophthalmos of the right eye, medium goitre with multiple nodules in the right lobe on ultrasound (1.1–1.7 cm, one 1.5 cm ill-defined, hypochocic, with small calcifications). TSH <0.03 mIU/L, high T3 and T4). She was treated with methimazole but lost to follow-up for 2 years. In 2011 she presents with overt hyperthyroidism and a large goitre, with a 4 cm ‘cold’ nodule in the right lobe with microcalcifications and internal vascularisation. She underwent total thyroidectomy and was diagnosed with multifocal papillary carcinoma: 3.3 cm in the right lobe, with capsular invasion, and 1.5 cm in the isthmus (‘follicular variant’). No metatases have been detected. The patient has received a total of 150 mCi 131I and is disease-free at 2.5 years of follow-up.

Patient 2. A 56-years-old woman, was diagnosed at the age of 35 with a thyroid nodule and then at the age of 56 with subclinical hyperthyroidism, normal TPOAb and a toxic nodular goitre with a 2 cm nodule with peripheral calcification in the right lobe and a 4 cm ‘hot’ hypochocic nodule of in the left lobe. She underwent}

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Gigantomastia with mastitis during pregnancy in a patient with well controlled thyroid and lupus disease – a case report
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Introduction
Gigantomastia is a rare condition characterised by excessive benign breast tissue growth that is thought to be a result of elevated physiological levels of circulating hormones (e.g. pregnancy), or an increased sensitivity of the breast tissue to such hormones. Isolated reports describe some medical conditions as precipitants (e.g. systemic lupus erythematosus (SLE)) or drugs (e.g. cyclopamine). Many will proceed to surgical intervention to improve physical and/or psychological suffering.

Case report
A 39-year-old woman of normal weight conceived with in vitro fertilisation therapy after a salpingectomy for ectopic pregnancy. She had well controlled Graves’ disease and SLE on medication. Shortly after her salpingectomy she noted a gradual increase in her breast size, correlating with her monthly cycle, from a brassiere cup size C to a size E at the time of embryo transplantation. During her pregnancy, her breast size continued to increase at such a rate that her brassiere size changed every 3 weeks. Empiric bromocriptine was started at 30 weeks gestation. At 33 weeks she required inpatient admission for mastitis and a urinary tract infection. At 34 weeks her ultrasound showed oligohydramnios, thought to be secondary to her excessive breast tissue, and so she underwent caesarean section. As she chose not to breastfeed bromocriptine was continued.

Conclusion
Gigantomastia is generally a rare, benign condition but is especially disabling to the pregnant woman. Excellent outcomes are generally achieved with surgery. To our knowledge this is the first documented case in a patient with thyroid disease.

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Exquisite case of coeliac disease in elderly patient with polyglandular autoimmune syndrome type III; a case report
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Introduction
The link between Celiac disease (CD) and type 1 diabetes mellitus is well known. CD is an autoimmune disorder which was considered as a disease of childhood. Now, we know that CD is life-long condition. It affects people of all ages and all body shapes. Screening for CD or type 1 diabetes is recommended in individuals already diagnosed with either disorder. When individuals have both diseases, type 1 diabetes is usually diagnosed first.

Objectives
Our aim is to demonstrate clinical case of CD in 40 years old woman and results of successful treatment of a Polyglandular Autoimmune Syndrome type IIIA (diabetes mellitus type 1, Hashimoto’s Thyroiditis and Celiac disease). Design and methods
40 years old woman, who has had diabetes mellitus type 1 since the age of 6 years, attended our clinic as her glycemia was poor controlled. She had episodes of severe hypoglycemia and complained of weakness, weight loss, fatigue, diarrhea 4–5 watery stools daily. Laboratory analysis were performed. Thyroid function tests revealed primary hypothyroidism, Hashimoto’s Thyroiditis. It was believed that she had chronic diarrhea due to her diabetes and Alpha Lipoic Acid, B vitamins, Actovegin was initiated. After 2 weeks occurred swollen abdomen and edema of lower extremities. Abdomen Ultrasound showed rush peristalsis of intestines, no liquid was observed. Biochemical profile was within normal range. CD was suspected as a disease frequently associated with Polyglandular Syndrome Type IIIA. The diagnosis of CD was confirmed by Serologic test for AGA and the biopsy. Gluten free diet was advised. After 2 weeks her diabetes was better controlled. She has no complaints of diarrhea. Conclusion
CD screening is recommended in elderly patients with Diabetes Mellitus type 1 as well as in children.

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TFN-α and adiponectin pathways are deregulated in endometria from obese women with polycystic ovarian syndrome
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Seventy percent of women bearing PCOS are obese; adiponectin and TNF-α, as obesity markers, have a dual role in the sensitivity and action of insulin. Adiponecit (insulin sensitising) decreases, whereas, TNF-α, IL6 (negative

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regulators of insulin pathway) increases in obese-women. Moreover, TNFα decreases the transcript and protein levels of adiponectin. These changes could affect the normal energetic status in endometrium, tissue that exhibits abnormal insulin signalling in the PCOS condition (hyperandrogenic/hyperinsulinic environment). The aim of the present work was to evaluate molecules involved in TNFα (RTNFα 1 y 2, NFκB, p-IKK) and adiponectin (AdipoR1, AdipoR2, APPL1, TAK1, MEK1) signalling in endometria (n = 15) from lean, Obese and Obese-PCOS women by western-blot, immunohistochemistry and real-time PCR. Also, the number of macrophages was evaluated by CD68 and plasma levels of adiponectin, TNFα and IL-6 were assayed by ELISA. No changes in serum TNF–α levels were observed, however, IL–6 levels increase in both Obese groups vs Lean (P<0.01). Adiponectin was lower in Obese-SOP (P<0.01). TNFα, its receptors and CD68 levels increase in Obese-PCOS vs other groups (P<0.05). Transcripts levels for adiponectin, TNFα/receptors and APPL1 were similar in the three groups of endometria. NFkB nuclear localization was higher in Obese-SOP vs the other groups (P<0.05) and activated IKK increased markedly in both groups of Obese vs Lean group (P<0.0001). Adiponectin protein levels (plasma and endometrial), AdipoR1, APPL1 and MEK1 were low in Obese-PCOS vs Lean group (P<0.05); TAK1 diminished in both Obese endometria (P<0.05). Consequently, there is an increased inflammatory environment in endometrium of Obese-PCOS women that could decrease adiponectin signalling, through the participation of TNFα, NFκB activation and/or IL–6 signalling; therefore, affecting insulin signalling under obesity, hyperandrogenic and hyperinsulinic conditions, compromising the energetic metabolism for normal endometrial function.

Disclosure
This study was supported by grants #1130053 from the Fondo Nacional de Desarrollo Científico y Tecnológico, Chile (to MV) and # 21120541 (to LO) from the Fondo Nacional de Desarrollo Científico y Tecnológico, Chile.

Introduction
Acanthosis nigricans is a condition commonly associated with disorders characterised by insulin resistance. Data regarding the treatment of acanthosis nigricans are still insufficient.

Case report
A 10-year-old overweight girl (BMI = 24 kg/m²) presented at the obesity outpatient clinic. Her family history was negative for metabolic syndrome. Clinical examination revealed extensive acanthosis nigricans involving the neck and armpit. Laboratory tests were normal except for HOMA-IR that confirmed insulin resistance (HOMA-IR = 14). The patient was started on hypocaloric diet and exercise without clinical improvement after 1 year. Acanthosis nigricans expanded involving neck, armpit and thorax, as insulin resistance increased (HOMA-IR = 28.6). Metformin at a dose of 1700 mg daily was added to the diet and exercise with good clinical response. Insulin resistance decreased significantly after 3 months (HOMA-IR = 5.85) and acanthosis nigricans regressed after one year of treatment.

Conclusions
Metformin may be an effective treatment option in some cases of acanthosis nigricans. Larger studies are necessary to establish the efficacy and safety of agents that reduce hyperinsulinaemia and insulin resistance in the treatment of acanthosis nigricans.

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EP1329
Functional analysis of four mutants of the V2 receptor
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Diabetes insipidus is a disorder characterised by severe liquid-imbalance because of the inability to concentrate urine. Inactivating mutations in either arginine vasopressin receptor type 2 (AVPR2) or aquaporin 2 (AQP2) gene can cause congenital Nephrogenic diabetes insipidus (NDI). AVPR2 is a G protein-coupled receptor (GPCR) and is mainly expressed at the basolateral side of the kidneys collecting duct principal cells. Activation of this receptor by vasopressin is responsible for elevation of cAMP levels resulting in insertion of AQP2 water channels in the cell membrane of the collecting duct cells. In this study, four new mutations of AVPR2 gene (R68W, R67_G69del/G107W, V162A and T273M) were found in patients and were functionally analysed. For this purpose, all mutants were generated by a site-directed mutagenesis strategy. Both, total cellular expression and cell surface expression of mutant receptors were analysed in ELISA experiments. Also, cAMP accumulation and concentration response curves were determined for each mutant receptor. According to total ELISA results, all mutant receptors were synthesised comparable to WT receptor. However, cell surface expression was impaired for all mutants except of V162A. cAMP measurement for mutant and WT receptors revealed reduced Emax values for all mutants. For some mutants (R68W, R67_G69del/G107W and T273M) concentration response curves showed shifted EC50 values to higher vasopressin concentrations. In conclusion, we characterised four new AVPR2 mutations found in Turkish patients. Some mutations lead to shifted EC50 values by only one magnitude and treatment with higher amounts of AVP could be helpful for these patients to reduce high urine volumes and to restore kidney function.

Disclosure
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EP1330
Diabetes, obesity and psoriasis in a 60-year-old woman
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A case of multiple gas-forming pyogenic liver abscesses in diabetic patient
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Background
Gas-forming pyogenic liver abscess is an uncommon, life-threatening infection that is usually found in poorly-controlled diabetic patients. Here, we experienced a case of gas-forming pyogenic liver abscess in diabetes caused by Klebsiella pneumoniae.

Clinical case
A 77-year-old man with 25-year history of diabetes was admitted due to fever for 2 days. On the physical examination, right upper quadrant tenderness of the abdomen was present. Initial laboratory results were: WBC 29 030/mm³ (Neutrophil 94.3%), C-reactive protein 19.21 mg/dl, Procalcitonin 12.3 ng/ml, Gas-forming pyogenic liver abscess is an uncommon, life-threatening infection that is usually found in poorly-controlled diabetic patients. Here, we experienced a case of gas-forming pyogenic liver abscess in diabetes caused by Klebsiella pneumoniae.

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Conclusion
The clinical outcome of gas-forming liver abscesses appears to be fatal, therefore, an early aggressive therapeutic strategies, such as percutaneous drainage or surgical intervention are needed.

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Diabetes, obesity and psoriasis in a 60-year-old woman
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1Internal Medicine Service, Hospital Virgen del Rocío, Seville, Spain; 2CIBER Epidemiología y Salud Pública, Seville, Spain.

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Conclusion
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Psoriasis (PS) is a skin disease of immune T-cell mediated. It is well known that obesity is a risk factor for severity PS and PS is associated with the degree of overweight. In addition, patients with PS have increased risk of metabolic disorders such as diabetes mellitus (DM) and dyslipidaemia. All these processes are characterised by the presence of systemic chronic inflammation. Liraglutide, an agonist receptor GLP-1, is being used in the treatment of obesity and diabetes mellitus with excellent results both in glycaemic control and reduced body weight.

**Case report**

60-year-old woman with a history of type 2 diabetes, type II obesity (78 300 kg; BMI 38.39) and moderate psoriasis which was derived from primary care for poor glycaemic control (glycated Hb: 7.3%). Skin: injuries erythematous scaly plaques on back of hands, elbows, knees, trunk and scalp with PASI 5.8 and BSA 7% (Fig. 1).

Treatment was initiated with metformin 850 mg bid and liraglutide 1.2 mg/s, reduction of 8.5 kg in weight and improvement of skin lesions with PASI <3 and BSA 2% (Fig. 2).

**Conclusions**

The improvement in the weight reduction and improved glycaemic control as well as reduced secretion of proinflammatory cytokines placed the receptor agonists of GLP-1 in a special place for treatment of patients with T2DM and psoriasis. These features, which have yet to be demonstrated on a consolidated basis in clinical practice, can play a key role in the individualization of treatment of patients with T2DM.

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**EP1331**

**Metformin and lactic acidosis: a potentially lethal relationship during intercurrent illness**

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**Introduction**

Metformin-associated lactic acidosis (MALA) is defined as a high anion gap metabolic acidosis with high circulating lactate levels and without hypoperfusion. It is associated with a mortality rate up to 50%. The reported frequency is 0.01–0.05/1000 patient-years, mostly in patients with predisposing factors (which affect its clearance or energy metabolism) such as altered renal function, congestive heart, hepatic and respiratory failure, concomitant medications (angiotensin II receptors antagonist), old age. We present a report of a patient with type 2 diabetes who was receiving long term treatment with metformin and developed severe metformin associated lactic acidosis after dehydration, which resulted in renal impairment and consequent accumulation of metformin. We want to remind of a potentially lethal adverse reaction of this drug.

**Case report**

Our patient was a 64-year-old Albanian woman with a 3 year history of type 2 diabetes mellitus (treated with metformin 850 mg/d) and hypertension (treated with losartan 50 mg/d). She presented to our emergency with acute renal, hepatic, circulatory failure and severe metabolic acidosis, after a week history of abdominal pain, vomiting (associated with poor oral intake) and dyspnoea. Her medication also compromised a 3 day history of clarithromycin for acute sinusitis. She took adequate supportive care, management of concurrent disease, correction of acidemia, acceleration of lactate metabolism, and interruption of the offending drug. Twenty-four hours later, full clinical recovery was observed, with return to a normal serum lactate level.

**Conclusions**

Our initial impression was that the multiorgan failure was due to a combination of factors, including poor oral intake and nephrotoxic agents. Dehydration in patients taking metformin can lead to MALA. Given that mortality metformin should always be discontinued in such a clinical scenario. This case illustrated the importance of stopping metformin treatment (even small dose) during intercurrent illness, especially dehydration.

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**EP1332**

**Leg oedema: first sign of an ischemic leg which precipitated hyperosmolar hyperglycemic state in a newly diagnosed type 2 diabetes patient**

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Patients with diabetes are prone to peripheral vascular disease. We present the case of an 81 year old female, current smoker who presented to her general practitioner with a 3 day history of ankle oedema for which she received furosemide. She had a background of right above knee amputation due to peripheral vascular disease and essential thrombocythaemia. Five days after commencing furosemide, she developed increased lethargy and confusion. On arrival to hospital, her venous blood glucose was 32.8 mmol/l, ketones of 1.8 mmol/l and she wasn’t acidotic. She was dehydrated with sodium of 159 mmol/l, urea of 9.5 mmol/l, creatinine of 43 μl. Calculated serum osmolality was 338 mOsmol/kg. Insulin infusion and fluids were commenced. HbA1c was 81 mmol/mol on admission, with no prior history of diabetes. She developed atrial fibrillation while inpatient requiring digoxin. She was found to have a pale, pulseless, cold, ischemic left leg and was considered to be a very high perioperative risk. After discussion with family, she was started on the palliation pathway. This is a rare presentation of acute leg ischemia in a patient with newly diagnosed diabetes. She likely had an ischemic left foot which was masked by leg oedema. Peripheral vascular disease patients, who keep their legs in a dependent position for comfort often present with considerable edema of the feet and ankles. Numerous factors could have contributed to the ischemia, including emboli from atrial fibrillation, essential thrombocythaemia and peripheral vascular disease. Conversely dehydration from HHS could have precipitated her atrial fibrillation.

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Endocrine Disrupting Chemicals and Health Effects: A Review

Endocrine disrupting chemicals are substances, both natural and artificial to which we are all exposed, even in a low dose in our everyday life. Health effects attributed to endocrine disrupting compounds include immune dysfunctions, various cancers, neurological effects and behaviour disorders, reproductive problems, early puberty, etc. Over the past 50 years, an increase in urogenital tract abnormalities in males has been noted. We present a 4 year old boy case report, born at term, by caesarean section, addressed to the Endocrinology Department for microopenis, hypophasias and overweight. His mother was diagnosed with PCOS but she never took anti androgenic treatment before the patient was conceived; she is working in a paint factory. The first consultation revealed: microopenis: 3 cm (< 2.5 DS), hypophasias, bilateral descended testicles and normal developed scrotum. Workup: normal pituitary function; DHEAS slightly increased: 5 cm; is scheduled for hypospadias correction intervention.

Conclusions

Endocrine disruptor pathology must always remain a diagnostic hypothesis in reproductive tract abnormalities in children.

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Intentional massive overdose with aspart and glargine insulin: a case report

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Intentional insulin overdose in diabetic patients is a rare critical situation. The severity is due to numerous neurological complications, electrolyte disturbances, liver and lung damage or death.

Case report

A 65-year old male, with significant cardiac and pulmonary pathology, diagnosed with type 2 diabetes since 1996 and treated with glargine (70 U/day) and aspart (68 U/day) insulin is admitted to our centre via ER (emergency room) after an episode of severe hyperglycaemia after administration of 750 U aspart insulin and 280 U glargine insulin. He arrived in the ER 3 h after overdose with a glycaemic value of 47 mg/dl after 40 ml of 33% glucose and 250 ml of 10% glucose. At admission: altered general status, blood glucose 105 mg/dl, tachycardia, multiple injection sites across his abdomen, acanthosis nigricans on the right elbow. Labs exams revealed: hypertriglyceridaemia, hypocalcaemia, slightly elevated creatine; ALT: 7.9%. An infusion of 20% glucose was begun at 83 ml/h. The glucose infusion rhythm and concentration was adjusted according to the glycaemic profile while maintaining values around 150 mg/dl, with a total duration of infusion of 61 h. Hypocalcaemia was corrected by i.v. administration of calcium gluconate. Electrolytes, phosphorus and magnesium remained within normal limits during hospitalization. Psychological and psychiatric evaluation diagnosed depression and emotional unstable disorder. To increase the insulin clearance i.v. Furosémide was given for 6 days. In the 5th day of hospitalization, we decided the conversion to oral therapy with metformin 2 g/day and sitagliptin 100 mg/day, with a good glycaemic control.

Discussions

Insulin overdose requires intensive and prolonged glycaemic monitoring to prevent recurrent hyperglycaemia due to an early cessation of i.v. therapy. The dose is not correlated with the severity of hypoglycaemia but with a prolonged hypoglycaemic risk higher than that deduced from the pharmacokinetics of insulin analogue administered. This case represents the largest overdose with this analogues treated only by glucose infusion.

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Severe osteoporosis as a presentation of concealed Swyer syndrome (pure gonadal dysgenesis)

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Swyer syndrome (pure gonadal dysgenesis) is characterised by female phenotype with a 46 XY genotype due to a mutation of the sex determining region (SRY) gene on the Y chromosome. A 28 year old presented with back pain after an accident and had a 2nd lumbar vertebral fracture and severe osteoporosis. The DXA scan T score was −4.2. Procollagen Type I pro peptide and Osteocalcin levels were high. She had been in good health and denied any family illness. She was 180 cm tall and weighted 63 kg. Breasts were present though not fully developed. She had sparse pubic and axillary hair. The external genitalia was normal. She had high gonadotropins and low oestradiol and testosterone levels. She had normal serum calcium, phosphate, parathyroid hormone, and vitamin D levels. coeliac and immunoglobulin screen was negative. She had no liver or renal disease. The patient reported menstruating from age 14. Genotype was 46XY -normal male. PCR analysis confirmed the SRY locus on the Y chromosome. MRI and ultrasound of pelvis showed a uterus, fallopian tubes, vagina and one streak gonad. Anti Mullerian factor was low. There is the first reported case of severe osteoporosis as the presentation of Swyer syndrome. It improved with a 29% increase in T score over 2 years with recombinant parathyroid hormone. She menstruated for the first time of cyclical oestrogen. She underwent gonadectomy for the risk of malignancy. Osteoporosis and tall stature were due to life long oestrogen deficiency. The patient later admitted she had concealed primary amenorrhoea for cultural reasons delaying early diagnosis and treatment.

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EP1337
Recurrent severe symptomatic hyponatraemia induced by low-dose oral cyclophosphamide in a patient with ANA-related vasculitis
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Cyclophosphamide is an alkylating agent used in the treatment of malignant and autoimmune diseases. Severe hyponatraemia is a serious electrolyte disorder with life threatening neurological sequelae. We report a case of recurrent, symptomatic hyponatraemia that developed in a 61 year old female with systemic vasculitis and Sjogrens syndrome following low-dose cyclophosphamide.

Case report
A 61 year old lady, with ANA positive systemic vasculitis presented for her first cycle of low dose cyclophosphamide (12 mg/kg). She was prehydrated with 1 l of normal saline and drank 3 l of water for prophylaxis of haemorrhagic cystitis. 30 h post treatment her serum sodium fell from 135 mmol/l pre-treatment to 116 mmol/l with decreased GCS, requiring ITU admission. Her urinary sodium was 121 mmol/l, urine osmolality 347 mOsm/kg with a plasma osmolality of 240 mOsm/kg. She received hypertonic saline and recovered without neuro-logical deficits after slow correction over 2 days. Four weeks later, she was admitted to hospital for careful monitoring, at her second cycle, she was again prehydrated. 24 h post treatment her sodium fell to 121 mmol/l with altered consciousness again requiring hypertonic saline. At her third cycle, she was not prehydrated and was commenced on a 1.5 l fluid restriction. Despite fluid restriction, her serum sodium fell from 135 to 129 mmol/l post therapy, without clinical features and corrected spontaneously.

Discussion
Patients receiving cyclophosphamide are at high risk of developing symptomatic hyponatraemia due to SIADH even at low doses of therapy. Cyclophosphamide may induce SIADH, by potentiating the renal actions of AVP. The combination of both increased ADH effect and excess water intake to prevent haemorrhagic cystitis can induce potentially life-threatening hyponatraemia. Clinicians need to be aware of this threat when encouraging large volume prehydration and diuresis with cyclophosphamide therapy. It is possible that pre-hydration with isotonic saline rather than oral water may minimise the incidence of this complication.

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EP1338
Polycystic ovary syndrome in women with type 1 diabetes mellitus: about three cases
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Introduction
Polycystic ovary syndrome (PCOS) is the most common endocrine disorder and is frequently associated with insulin resistance and type 2 diabetes mellitus. At present, women with type 1 diabetes mellitus (T1DM) are being treated with supraphysiological doses of exogenous insulin with the aim of providing a strict metabolic control. The prevalence of PCOS in women with T1DM varies depending on the diagnostic criteria employed and on the ethnicity of the population studied. In 2000 Escobar-Morreale et al., using National Institutes of Health (NIH) 1990 diagnostic criteria, reported a prevalence of 18.8%.

Design
We’ll describe three profiles of PCOS in women (age 34, 31, 30 years old) with T1DM that is controlled by high dose of insulin. They have a normal level of SHBG. The PCOS is treated by modification in life style and metformin therapy.

Results
The physiopathology of PCOS in T1DM is unclear. It has been suggested that the use of exogenous insulin at high doses daily to treat T1DM may contribute to the development of PCOS by stimulating the synthesis of ovarian androgens. The normal levels of SHBG in T1DM (insulin concentrations at the portal vein are the main regulators of SHBG) explain both why the most sensitive serum marker of hyperandrogenism here is total testosterone levels, and the milder hyperandrogenic symptoms. The use of metformine permits a significant reduction in the insulin dose administered while providing an improvement in metabolic control.

Conclusions
Every effort must be made for the early detection and treatment of hyperandrogenic disorders in T1DM women because of the large prevalence of PCOS in these women. Future studies should evaluate the consequences of PCOS in women with T1DM and compare the different therapeutic options.

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EP1339
A case of Swyer syndrome with gonadoblastoma and dysgerminoma
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Aim
The Swyer syndrome belongs to a group of pure gonadal dysgenesis. Karyotype is 46,XY. Aberrations of chromosome Y or SRY gene mutation is present in 15–30% of cases. These patients have high gonadotropin levels and are classified as having hypergonadotropic hypogonadism. The Swyer syndrome in the female requires close followup because of the high risk of neoplastic transformation in the dysgenetic gonads. Herein we report a case of Swyer syndrome with gonadoblastoma and dysgerminoma.

Case
A 22-year-old woman was admitted to the Endocrinology Outpatient Clinic. Menarche age was 15 years old. Breast development was normal during pubertal period without using any oestrogen pill. After 1 year of regular menstrual period, irregular vaginal bleeding occurred. At the age of 18, a big mass was felt on abdomen. She had an abdominal operation for that mass and gonadoblastoma and dysgerminoma were diagnosed pathologically on the right ovary. After that pathologic diagnosis, karyotype study was performed and found as 46,XY. As the integrity of tumour capsule was destroyed, adjuvant chemotherapy was introduced. After chemotherapy, another abdominal operation was performed and gonadoblastoma was diagnosed on the left ovary. There was no laboratory examination regarding to gonadotropin and oestrogen levels before the operations. SRY positivity was present on left oophagectomy material.

Phenotypically female patient with 46, XY karyotype, Swyer syndrome was diagnosed. She was started estrogen/progesterone combination pill.

Discussion
This patient had the normal pubertal development without any delay. Because of this reason, we thought that the gonadoblastoma was hormone active most probably with oestrogen producing one. Unfortunately, we couldn’t demonstrate this. Patients with gonadal dysgenesis and 46,XY karyotype should be referred for bilateral gonadectomy because of the high risk of neoplastic transformation. Oestrogen producing gonadoblastoma may mask gonadal dysgenesis and delay the diagnosis of this pathology.

Conclusions
We present here a case of a young Filipina who presented with multiple fractures on all extremities and bilateral parathyroid adenoma.

Case presentation
A 19-year-old Filipina presented with bone pains for 7 months associated with fatigue, anorexia, weight loss and muscle weakness. Subsequently, she had multiple fractures on all extremities and fixed hard masses on the left hemerus and tibia. Her past medical and family histories were unremarkable.

Investigations
Corrected calcium was elevated at 15.4 mg/dl, Phosphorus was decreased at. Intact PTH (iPTH) was extremely high at 2001 pg/ml (8.5–72.5). X-ray of the tibia. Her past medical and family histories were unremarkable.

Introduction
Parathyroid carcinoma is a rare cause of hyperparathyroidism. In most cases, hyperparathyroidism is caused by a single benign adenoma. The vast majority of the remaining cases are caused by parathyroid hyperplasia or multiple adenomas. We present here a case of a young Filipina who presented with multiple fractures on all extremities and bilateral parathyroid adenoma.

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Conclusions
We present here a case of a young Filipina who presented with multiple fractures on all extremities and bilateral parathyroid adenoma.
extremities showed osteopenia, endosteal resorptive changes and multiple pathologic fractures. Bone biopsy revealed brown cell tumour/multifocal polyostotic giant cell tumour and negative for malignancy). Ultrasonography of the neck revealed parathyroid adenoma inferiorly of the left lobe and measuring 2.3 x 1.1 x 1.0 cm. Ultrasound-guided FNA revealed findings consistent with parathyroid carcinoma. She was hydrated and was given diuretic to control the severe hypercalcaemia. She underwent 3/4 gland parathyreidectomy with en-bloc thyroid lobectomy. Intraoperative findings showed a left mass with non-well-circumscribed borders invading the capsule and local tissues and a right mass. Serum Calcium and iPTH immediately after OR decreased to 12.8 and 211.8 pg/ml respectively. Further reduction was noted after 24 h of surgery (iPTH, 48 pg/ml; Corrected Calcium: and 9.2 mg/dl).

Discussion/Conclusion

Parathyroid carcinoma is a rare malignancy of the parathyroid glands. These tumours usually secrete parathyroid hormone, thereby producing hyperparathyroidism, which is usually severe. Surgery with en-bloc resection is the initial therapy, but when the tumour is no longer amenable to surgical intervention with intent to cure, treatment becomes focused on the control of hypercalcaemia.

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EP1341

An aggressive malignant insulinoma: a case report

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Introduction

Insulinomas are rare pancreatic islet cell tumours with an incidence of four cases per million per year. About 10% of all insulinomas are malignant. We here examined an insulinoma with aggressive driving in a young male patient with severe hypoglycaemia in the emergency room.

Case report

34-year-old male patient was admitted to the emergency department with the blurring of consciousness. Blood glucose was 3 mg/dl, consciousness tends to sleep, non-cooperative and disoriented. Continuous dextrose infusion was required and the patient’s laboratory tests results: aspartate aminotransferase (AST) 132 U/l, alanine aminotransferase (ALT) 225 U/l, γ-glutamyltransferase (GGT) 504 U/l, alkaline phosphatase (ALP) 315 U/l, albumin 3.7 g/dl, total bilirubin 3.3 μg/dl, direct bilirubin 1.9 μg/dl, respectively. When the dextrose infusion interrupted, the blood glucose was 32 mg/dl whereas insulin level was 110 μIU/ml (n = 0.29–1.7 μIU/ml) and C-peptide level was 5.6 ng/ml (n = 0.9–4.3) respectively. Serum chromogranin A level was 158 ng/l (27–94). Magnetic resonance imaging of the brain showed multiple small hypointense lesions. Magnetic resonance imaging of the spine showed no signs of masses. Continuous dextrose infusion was initiated.

Conclusions

A clinical redefinition of diagnosis was made: VIPoma. Hypercalcemia might be explained by the stimulatory effect of VIP on bone resorption. However, if normal feedback is intact, PTH concentrations should be low, whereas the patient described had a ‘normal’ PTH. We have observed a sustained response of calcium levels since cinacalcet introduction. 5% of VIPomas are in context of MEN-1.

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VIPoma: an unusual cause of electrolyte disturbance

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Introduction

Vasoactive intestinal peptide-producing tumours (VIPomas) represent a rare type of neuroendocrine tumour whose incidence is 1 in 10 million per year. Most are located in the pancreas. They cause diffuse watery (secretory) diarrhoea, hypokalaemia and achlohydria and also appear as an uncommon cause of hypercalcaemia.

Case report

A 69-year-old female with previous diagnosis of a ‘non-functioning’ neuroendoctrine pancreatic tumour (2005) with liver metastasis (2009) was admitted for weakness and severe hypokalaemia. She had been admitted for hypercalcaemia a few months before. Her family history was a priori negative for MEN-1 affected. She complained of chronic watery diarrhoea that persisted with fasting (6–10 stools/day) in spite of multiple therapies (surgery, long acting somatostatin analogues, systemic chemotherapy and transarterial hepatic chemoembolization). Analysis showed: impaired fasting glucose (159 mg/dl), hypokalaemia (2.6 mEq/l), metabolic “acidosis” (pH 7.34, serum bicarbonate 15.1 mEq/l), hypophosphatemia (1 mg/dl); hypomagnesemia (1.6 mg/dl) and hypercalcaemia (until 15.3 mg/dl). Serum TSH, calcitonin, cortisol, PRL, glucagon, PTH-rp and 5HIAA were normal. PTH 23.8 pg/ml. 25-OH-vitamin D 35.6 ng/ml. Ca×Al 115 ng/ml. VIP concentrations were high (>110 pmol/l normal <30 pmol/l). Gastrin 149 pg/ml (13–115). An octreoscan showed known liver disease. There were no bone metastases. Immunohistochemistry was positive for somatostatin, synaptophysin and chromogranin A. Patient needed to be managed with high doses of supplements of potassium, magnesium, phosphorus, periodic i.v. bisphosphonates and a high salt intake. Recently, an essay of cinacalcet was added because of persistent hypercalcemia.

Discussion

A clinical redefinition of diagnosis was made: VIPoma. Hypercalcemia might be explained by the stimulatory effect of VIP on bone resorption. However, if normal feedback is intact, PTH concentrations should be low, whereas the patient described had a ‘normal’ PTH. We have observed a sustained response of calcium levels since cinacalcet introduction. 5% of VIPomas are in context of MEN-1. 

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probably evolving for a long time in the past, which was initially considered and treated as sarcoidosis.

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**EP1344**

Endocrine assays in female patient with relapsing thymus cyst and myasthenia gravis

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Introduction

The congenital cystic neck masses underlie various diagnosis including thymic cysts. Even they are an embryological defects, the adult onset might be seen. The aetiology is not clearly established. The malignant behaviour or infections are correlated to the cysts. Aim: we present a female case with a complicated history of cysts.

Case report

A 42-year-old female is known with the following medical history. Seven years ago she was operated for a pericardia cyst. The computed tomography was normal after surgery until 2014 when she accused breathing difficulties. The computed tomography was performed and a tumoral mass was discovered (of 7 cm). Thoracotomy was chosen as procedure for the cyst: the cyst was totally evacuated during the procedure and then removed but the thymus was conserved. The pathological examination confirmed a simple thymic cyst, with no atopia. After surgery, the patient felt well for about 6 months when she accused again troubles breathing, and also persistent asthenia. The computed tomography found again the thymic cyst of 4.89 by 4.1 by 6.4 cm, with no other thoracic or cervical anomalies. The patient was referred for an endocrinological check up. The blood pressure was 100 by 65 mmHg. The normal TSH of 1.5 μU/ml was associated with negative thyroid antibodies. The morning plasma cortisol was of 19 μg/dl (normal levels < 21 μg/dl). The calcium levels and parathormone, as well as basal plasma metanephrines/normetanephrines were also normal. The prolactin levels were mildly increased (of 28 ng/ml, normal levels < 22 ng/ml). The patient was referred to neurological tests and myasthenia gravis was confirmed. A second procedure for the thymus cyst is soon to be done, including the entire organ resection.

Conclusion

The mildly increased prolactin levels are most probably associated to the thoricic surgery. The complete resection of the thymus is encouraged in case of cysts, especially large ones, because of relapse risk.

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**EP1345**

Oncogetic osteomalacia misdiagnosed as ankylosing spondylitis

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Oncogetic osteomalacia is a rare paraneoplastic syndrome, which can be associated with phosphaturic mesenchymal tumor or non-mesenchymal tumour. This tumour produces fibroblast growth factor 23 (FGF-23) that leads to subsequent hypophosphataemic osteomalacia. We, hereby present a patient with oncogetic osteomalacia who is misdiagnosed as ankylosing spondylitis. A 54-year-old man with weakness, severe arthralgia involving pelvis, hip joints and lower extremities referred to the Rheumatology Department for the treatment of a suspected soro-negative spondioarthritis and TNF-α inhibitor and glucocorticoid treatment had begun. Despite of 3 years of treatment, there was no relief of symptoms, and laboratory tests had shown hypophosphatemia (0.7 mg/dl) with low vitamin D and normal calcium, PTH levels, referred to Endocrinology clinic. Hypophosphataemia was resistant to oral phosphate replacement. Physical examination revealed a non-tender, mobile, 2 cm nodular lesion at right medial thigh. Magnetic resonance imaging showed an oval 2.1×1.7 cm hypointense solid lesion with irregular borders in the soft tissue at right thigh. FDG-PET scanning showed high FDG uptake at the lesion, and no other hypermetabolic masses. We performed tumour resection and after an remarkable post-operative course hypophosphatemria resolved within 2 weeks. Histopathological examination showed extrasosseous giant cell tumour with metaplastic bone cell formation. After surgical removal patient’s symptoms have revealed and phosphorous levels became to normal levels. Oncogenic osteomalcia and ankylosing spondylitis, both can present with arthralgia, weakness, difficulty in walking. For the patients who have features suggestive of oncogetic osteomalacia, it is of crucial importance to perform a survey to detect the tumour or tumours responsible.

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**EP1346**

Stromal tumour revealing a multiple endocrine neoplasia type 1

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Gastrointestinal stromal tumour (GIST) is now defined as a specific, KIT-expressing and KIT-signalling driven mesenchymal tumour of the gastrointestinal (GI) tract. We report a case of stromal tumour revealed by prolonged fever and skin lesions associated with primary hyperparathyroidism and pituitary adenoma.

Observation

We present the case of a 59-year-old patient admitted for prolonged fever with inflammatory syndrome and latent cutsaneous lesions. Abdominal ultrasound showed two intra abdominal masses of the left hypochondrium and inter-spleno kidney. Their scanno guided biopsy concluded to a double localisation of a gastrointestinal stromal tumour CKIT+. The dermatological examination found a paraneoplastic dermatosis. The patient was put under Glivec 400 mg/day. A cervicothoracic CT discovered lung nodules. The colonoscopy found a juxta appendiceal tumour with multiple layered flat lesions which the biopsy concludes to a tubulo-villos adenoma with high-grade dysplasia. Hypercalcaemia 2.9 mmol/l is discovered. The diagnosis of primary hyperparathyroidism is confirmed by high PTH 217 pg/ml. A type 1 multiple endocrine neoplasia is evoked. A pituitary MRI found a micro pituitary adenoma. Hormonal exploration has concluded that it was a non-secreting adenoma. An abdominal CT scan finds a nodular hypertrophy of the left adrenal. The dosage of urinary Metanephine was normal. This case illustrates the possible association of a stromal tumour with MEN1.

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**EP1347**

Gastrinoma with liver metastasis; is it always a bad news?

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Introduction

Gastrinoma is a rare neuroendocrine tumor and associated with liver metastasis in 20–40% of cases. We present a rare case report of a patient with stable liver metastasis due to gastrinoma for more than 35 years.

Case report

A 49 year old male is currently on our regular clinic follow up for the liver metastasis due to gastrinoma. His past history includes open laparotomy and resection of gastrinoma (Proven histologically) at the age of 12. During the surgery liver metastasis was noted. He was followed up in clinic until the age of 20. Later he presented with diarrhoea at the age of 38 and was started on Omeprazole 20 mg TDS. Currently he has no symptoms. Genetic study for MEN-1 syndrome is negative. Blood tests showed raised Gastrin levels of 450 ng/l while on Omeprazole. MRI of abdomen in 2014 showed three large liver lesions with largest lesion size of 7 cm. Gallium Dotate PET scan showed all lesions are metabolically active. Compared to previous CT scan in 2006 and 2010 no change in the liver metastasis size.

Discussion and conclusion

Presence of liver metastasis with gastrinoma generally indicates poor prognosis with some studies suggests 10-year survival rate of only 10–20%. However very indolent gastrinoma with liver metastasis is rare and could be managed conservatively.

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EP1349
The effect of self-administration of Ipstyl treatment on patients’ lives: a qualitative study of patients with acromegaly
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In 2014–2015, a study of patients’ quality of life after training in self-management of monthly Ipstyl injections is implemented. These injections were previously given by their GPs. Inclusion criteria are described. Sample cuts across gender and age. Ten patients did not respond to mailed offers and 12 did not participate. The reason for this is only known to some of them. Six patients wanting training are invited to an introduction of self-management of Ipstyl and are informed that they can always turn to the department with questions related to self-management. Research interviews were conducted in connection with training. The Data Protection Agency approved the project, and the patients were informed of the rules for participation. An interview guide with validated questions was used, and qualitative interviews have so far been completed by two patients. Interviews of ~40 min were recorded and transcription carried out by the researcher. The patients’ statements are categorised and analysed according to Steiner Kvale’s analysis model’s three operational levels i) the patient’s self-understanding, which is a compressed image of the person’s perception, ii) critical sense, a broader frame of reference than the patient’s own opinion and iii) the theoretical level, providing a framework for interpretation of the meaning of statements (Kvale & Brinkmann 2009: 237ff.). The project’s most spectacular preliminary findings are: i) Independence in planning GP consultation; ii) critical sense, a broader frame of reference than the patient’s own opinion and iii) the theoretical level, providing a framework for interpretation of the meaning of statements (Kvale & Brinkmann 2009: 237ff.). The project’s most spectacular preliminary findings are: i) Independence in planning GP consultation; ii) critical sense, a broader frame of reference than the patient’s own opinion and iii) the theoretical level, providing a framework for interpretation of the meaning of statements (Kvale & Brinkmann 2009: 237ff.).

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EP1350
Continuous subcutaneous hydrocortisone infusion replacement treatment in adrenal insufficiency – how to start the hydrocortisone infusion
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Many patients with primary adrenal insufficiency (Addison’s disease) take extra doses of glucocorticoids before or during stressful events, but benefit has not been demonstrated. We aimed to test the effect of an extra dose of glucocorticoids on cardiorespiratory, hormonal and metabolic parameters in response to physical activity in a randomised placebo-controlled, 2-weeks cross-over, clinical trial (clinicaltrials.gov NCT01847690). Ten women with Addison’s disease and ten female controls participated in the study. All underwent maximal incremental exercise testing. A stress dose of 10 mg hydrocortisone or placebo was given 1 h before exercise on two occasions. Blood samples were drawn before, and at 0, 15 and 30 min post exercise. The glycaemia was followed by continuous glucose monitoring for 24 h. The primary endpoints were oxygen uptake (O2 uptake), maximal aerobic capacity (VO2 max). Secondary outcomes were detailed ergometric parameters, and duration of exercise, post-exercise hypoglycaemic events and glycaemic variability, endocrine and metabolic responses to physical activity, and health status evaluated by questionnaires. V02 max and duration of exercise were significantly lower in patients compared to controls and did not improve with the treatment. Stress-dosed hydrocortisone elevated serum cortisol significantly (cortisolmax mean 671 nmol/l (s.d. 49) vs 204 nmol/l (s.d. 41), P<0.0001). After exercise the blood glucose and adrenaline levels were significantly lower, and free fatty acids slightly higher, in the patients than in the controls, irrespective of stress dose. No differences were found between the treatments in metabolic or hormonal parameters or quality of life after the exercise. In conclusion, patients did not obtain benefits from stress-dosed hydrocortisone during strenuous short-term exercise. And such dosing does not seem justified in this setting.

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EP1351
Offspring of nurses working on irregular shifts are more likely to be underweight and less likely to be obese compared with those working on a regular basis
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Introduction
Like many other hospitals nurses work either on irregular shifts or on regular basis in our centre. Also their education levels differ among them. In this study we aimed to analyse some factors which may affect the children of female nurses’ adiposity.

Subjects and methods
We included 100 children of female nurses on duty in our hospital. The ages ranged between 2 months and 17 years. Results
According to standard BMI percentiles, 13 (13%) were underweight, 53 were normal weight (53%), 14 were overweight (14%) and 20 were obese (20%). Fifty seven were the first child (57%), 38 (38%) were the second and 5 (5%) were the third child. Sixty-eight children were born normally and 32 by caesarean section. Mothers of 42 children were working on regular basis compared with 58 working on irregular shifts. Out of the mothers of 13 underweight children 12 were working on irregular shifts and one on regular basis. Similarly out of the mothers of 20 obese children 12 were working on regular basis compared to eight on irregular shifts. These findings were statistically significant (P=0.016). Children’s adiposity were also positively associated with snack habits (P=0.003). There was no association between children’s adiposity and mothers’ education level, fathers education level, fathers working status, duration of breast feeding, birth weight, children’s gender, birth order, time of consumption of additional food and type of birth.

Conclusion
The main finding in our study was that underweight children were from mothers working on irregular shifts and that obese children were from mothers working on a regular basis. This could be attributed to irregular working hours leading to irregular and possibly insufficient family feeding. The mother is generally not with the child at feeding hours. These findings need to be clarified in larger scale studies.

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EP1352
Pegvisomant home care programme leading to rapid IGF1 control likely improves quality of life
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Background
Pegvisomant has demonstrated efficacy in attaining IGF1 normalisation in previously uncontrolled acromegalic patients. A home care programme improves treatment compliance.

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Aims
Evaluation of home educational program and quality of life (Qol).

Methods
Multicentre observational study involving eight Flemish centres. Uncontrolled acromegalic out-patients were trained for daily subcutaneous pegvisomant injection at home by one specialist nurse during 2 h. Enhanced motivation was provided through regular follow-up visits on day 2, 3 and 7 (60°, and twice 45°, respectively) and 15° phone calls at month 1, 1.5, 3, 4.5, 6, 12, 18, 24, 30 and 36. Preliminary results include IGF1 at baseline, 3, 4.5, 6, 12 and 18 months. Qol was assessed by Patient-Assessed Acromegaly Symptom Questionnaire (PAQ15).

Results
Eighteen patients were included. Associated treatments were long-acting somatostatin analogues (n=15): five patients were treated with octreotide LAR 30 mg monthly, four patients with lanreotide 90 mg monthly and six patients with lanreotide 120 mg monthly. In all participants, IGF1 decreased (sometimes needing dose adjustment of pegvisomant from 10 mg OD to 30 mg OD) and Qol improved significantly over time (P<0.001), based on decreased complaints of headache (P=0.002), perspiration (P=0.001), joint pain (P=0.007), fatigue (P=0.023) and soft tissue swelling (P=0.001). These improvements were durable and no drop-outs were observed Table 1.

Conclusion
Working with a specialist nurse may help to improve Qol by attaining rapid IGF1 normalisation, due to enhancing patients’ compliance. PAQ15 score improved both on short and longer term.

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Table 1

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<th>Baseline (n=18)</th>
<th>3 months (n=18)</th>
<th>4.5 months (n=12)</th>
<th>6 months (n=9)</th>
<th>12 months (n=11)</th>
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<td>IGF1 (ng/ml)</td>
<td>464 ± 262</td>
<td>221 ± 103</td>
<td>282 ± 236</td>
<td>249 ± 167</td>
<td>217 ± 136</td>
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<th></th>
<th>Baseline (n=11)</th>
<th>1 month (n=18)</th>
<th>6 months (n=15)</th>
<th>12 months (n=10)</th>
<th>18 months (n=9)</th>
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<tr>
<td>PAQ15 (0–8)</td>
<td>11 ± 7</td>
<td>7 ± 6</td>
<td>6 ± 6</td>
<td>5 ± 5</td>
<td>3 ± 3</td>
</tr>
</tbody>
</table>

Conclusion
Even after Master studies, the level of knowledge of nurses about prevention of work accidents, post-exposure prophylaxis and competency in special nursing fields is unsatisfactory. These results raise the need for the development of national standards in general nursing and the need for professional accreditation of skills and knowledge into practice. We should focus on work-based and lifelong learning plus supervisions. Specialist nurses may achieve the expert status, in those competencies relevant to them, after 5 years and more in their specialty.

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