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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 Prof. Martin Fassnacht. The prize will be presented as part of the ECE 2014 opening ceremony where Prof. Fassnacht will deliver his lecture. Prof. Fassnacht will also write a review article based on this lecture to be published in the *European Journal of Endocrinology*.

Martin Fassnacht, Germany

Prof. Martin Fassnacht was born in 1971 and studied medicine at the Saarland University and the University of Würzburg. He started his research on adrenal tumors in 1995, when he joined the Würzburg Endocrine Unit for his doctoral thesis. He then completed a two year post-doctoral fellowship at the Duke University in the US and returned to Würzburg to complete his medical training for internal medicine and later for endocrinology and diabetes under the mentorship of Prof. Bruno Allolio.
In 2006 Martin Fassnacht was appointed consultant endocrinologist and in 2008 deputy head of the Department of Endocrinology at the University Hospital of Würzburg.
In 2012 he became Professor at the University of Munich and Head of Clinical Endocrinology, the Center for Endocrine Tumors at the University Hospital of Munich. Just recently, in February 2014, he was recruited by the University of Würzburg and is now head of its Department of Endocrinology and Diabetes. Prof. Fassnacht has published more than 130 articles in peer-reviewed journals including several outstanding reviews. He is a clinical scientist with a special focus on adrenal diseases and endocrine oncology. Research in his laboratory aims at a better understanding of the pathogenesis of adrenal tumors and new treatment strategies for adrenocortical carcinoma. He has run several clinical trials for different endocrine tumors, including the first randomized trial for adrenocortical carcinoma, FIRM-ACT.
Prof. Fassnacht has received a number of awards, including the Marius-Tausk Price 2003 and the Schoeller-Junkmann Award 2010 of the German Society of Endocrinology as well as the AIO Clinical Research Award 2012 of the German Cancer Society. He is currently the head of the Adrenocortical Carcinoma working group of the European Network for the Study of Adrenal Tumours (ENSAT) and serves as member of the Publication Core Committee of the American Endocrine Society and on the Clinical Committee of the European Society of Endocrinology.

The *European Journal of Endocrinology* Prize Lecture

Adrenocortical carcinoma – current concepts and future perspectives

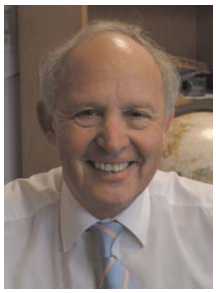
Martin Fassnacht, Department of Endocrinology and Diabetes, University of Würzburg, Würzburg, Germany

Adrenocortical carcinoma (ACC) is not only a rare and heterogeneous disease but also one of the most aggressive endocrine tumors. Despite significant advances in the last decade, its pathogenesis is still only incompletely understood and overall therapeutic means are unsatisfactory.
During this lecture, we provide our personal view of the currently available treatment options and suggest the following research efforts that we consider timely and necessary to improve therapy: i) For better outcome in localized ACC, surgery should be restricted to experienced centers, which should then collaborate closely to address the key surgical questions (e.g. best approach and extent of surgery) in a multi-center manner. ii) For the development of better systemic therapies, it is crucial to elucidate the exact molecular mechanisms of action of mitotane. iii) A prospective trial is needed to address the role of cytotoxic drugs in the adjuvant setting in aggressive ACC (e.g. mitotane vs. mitotane + cisplatin). iv) For metastastic ACC, new regimens should be investigated as first-line therapy. v) Several other issues (e.g. the role of radiotherapy and salvage therapies) might be answered – at least in a first step – by large retrospective multicenter studies. In conclusion, although complete understanding of ACC and cure in the majority of ACC is unrealistic within the next decade, international collaborative efforts (including multiple translational and clinical studies) should allow significant improvement of clinical outcome of this disease. To this end, it might be reasonable to expand the European Network for the Study of Adrenal Tumors (ENSAT) to a truly worldwide international network – INSAT.

Geoffrey Harris Prize Winner

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. Ashley Grossman. The prize will be presented as part of the ECE 2014 opening ceremony where Prof. Grossman will deliver his lecture. Prof. Grossman will also deliver two other lectures at future ESE scientific meetings. Further information can be found at http://www.ese-hormones.org/prizes/

Ashley Grossman, UK



Ashley Grossman initially graduated with a BA in Psychology and Social Anthropology from the University of London, then entered University College Hospital Medical School in London and took the University Gold Medal in 1975. He also obtained a BSc in Neuroscience. He joined the Department of Endocrinology at St Bartholomew's Hospital where he spent most of his career, eventually as Professor of Neuroendocrinology, but has recently moved to become Professor of Endocrinology at the University of Oxford in the Oxford Centre for Diabetes, Endocrinology and Metabolism. In 2000 he was appointed a Fellow of the Academy of Medical Sciences. In 2011 he was made a Fellow of Green-Templeton College at the University of Oxford. He has published more than 750 research papers and reviews.

He has a major interest in tumours of the hypothalamo-pituitary axis, especially Cushing's disease, but his clinical concern and research has expanded increasingly to include broad areas of endocrine oncology, most especially neuroendocrine tumours of all types, including phaeochromocytomas, paragangliomas, adrenocortical cancer, medullary thyroid cancer and hereditary endocrine tumour syndromes. In terms of basic research, he has developed many studies on hypothalamic regulation, eventually exploring the interaction between the hypothalamus and the immune system in terms of cytokines and gaseous neurotransmitters. However, for the last decade he has focused on the molecular pathogenesis of pituitary, adrenal and neuroendocrine tumours.

He is Past-President of the European Neuroendocrine Association (ENEA) and of the UKI Neuroendocrine Tumour Society (UKINETS), Chairman of the European Neuroendocrine Society (ENETS) Advisory Board, and President of the Society for Endocrinology. He is past editor of the journal *Clinical Endocrinology*, on the editorial board of the major textbook De Groot and Jameson's *Endocrinology*, is Vice-Chairman of the major online textbook *Endotext.org*, and serves on the editorial boards of many journals.

Geoffrey Harris Prize Lecture

Did the hand, then, of the potter shake?

A Grossman, Oxford, UK

Pituitary adenomas are not rare, with a prevalence of around 1/1000 population. However, their pathogenesis has defied decades of careful study. Many groups including our own have shown a plethora of changes within these tumours, with silencing, often epigenetic, of many tumour suppressors, suggesting activation of a pro-proliferative programme. However, apart from the Milan group's Gsp mutation in somatotrophinomas no single mutational oncogenic event has been demonstrated. Many of the transcriptional and cell cycle-related changes appear to be secondary to overdrive of cell signalling pathways, but analysis of growth patterns does not indicate a step-wise series of oncogenic changes, but rather a growth process leading to a new steady state modulated by cell surface contact. In an analogous situation of a benign tumour with growth interrupted by long periods of quiescence, adamantinomatous craniopharyngiomas have been shown to contain clusters of cells which have stem cell characteristics. Many of these tumours, probably the great majority, show activating mutations of the proto-oncogene β-catenin, but the mutation is widespread and the translocation of β-catenin to the nucleus only occurs in the stem cells. In papillary craniopharyngiomas the dominant mutation is of BRAF. In animal models these mutant stem cells give rise to secondary tumours, and one may speculate that a similar process may occur in non-functioning pituitary tumours (NFPAs). Whole-exome sequencing of NFPAs reveal a different oncogenic mutation in each tumour, which does not generalise to other tumours. It is therefore hypothesised that NFPAs arise from stem cell mutations which lead to localised proliferation with no common oncogenic denominator: the stem cell originators may be sparsely present or even absent at the time of tumour presentation. Indeed, the origin of pituitary adenomas my lie far back in past development, the 'potter's hand' having shaken in early embryogenesis or soon after.

Plenary Lectures

Genes, environment and endocrine disease

PL1

Genetics, environment and endocrine diseases

Jose M Ordovas
JM-USDA-HNRCA-Tufts, Boston, Massachusetts 02111, USA.

Current knowledge supports the notion that the onset and progression of endocrine and age-related diseases depend on an individual's metabolic flexibility. With respect to cardiometabolic diseases, especially in older persons, several factors act in concert and converge to challenge metabolic flexibility. These include an inadequate diet, insufficient physical activity, chronodisruption, decreased metabolic reserve, altered gut microbiome, and reduced immune system capacity. At the personal level, all these factors interact together and with an individual's genetic make-up to either promote or disrupt a program of metabolic flexibility in the context of endocrine disorders, aging, and obesity as well as the end point of many of these ailments, which are cardiovascular diseases.

Specifically, within the context of personalized nutrition or nutrigenomics, we seek to identify new metabolite-based markers, substantiate intake of certain foods, nutrients or dietary patterns, define the degree and mechanisms by which circadian control affects cardiometabolic diseases, and to describe the roles of microRNAs in these diseases.

Excellent examples of progress in this area are the results obtained for i) the APOA2 locus, dietary fat and obesity; ii) the LPL locus, polyunsaturated fatty acids, and triglyceride levels; and iii) the TCF7L2, Mediterranean diet and stroke. The results of the studies undertaken to date, indicate that huge progress has been made in identifying polymorphisms in genes related with endocrine and cardiometabolomic diseases. Therefore, while the current scientific evidence level of applying genotype data to personalized treatment is at its early stages, future prospects are encouraging. Outcomes of this research will generate new and better strategies for the prevention of age-related disorders and for slowing the aging process using nutritional and behavioral approaches.

DOI: 10.1530/endoabs.35.PL1

Advances in molecular pathogenesis of thyroid cancer – therapeutic implications

PL2

Advances in molecular pathogenesis thyroid cancer: therapeutic implications

Pilar Santisteban[1], Ana Sastre-Perona[1], León Wert-Lamas[1] & Garcilaso Riesco-Eizaguirre[1,2]
[1]Biomedical Research Institute, CSIC-UAM, Madrid, Spain; [2]Hospital Universitario De Mostoles, Madrid, Spain.

Thyroid cancer is one of the endocrine pathologies whose incidence is increasing, although in general terms it has a good outcome. However, some patients develop aggressive forms that are untreatable and the molecular basis is poorly understood. These aggressive forms are basically well-differentiated thyroid carcinomas that undergo dedifferentiation and poorly differentiated and anaplastic carcinomas. All of them have lost Na/I Symporter (NIS) function leading to radioiodine-resistant metastatic disease. Recent advances have contributed to a better understanding of the pathogenesis of these types of tumors. The genetic changes that activate the signaling cascade RET-RAS-BRAF are well known. The oncogenic BRAF mutation is a frequent genetic event that confers aggressive biological behavior to papillary thyroid cancer and has been associated to increased mortality. We have demonstrated that BRAF impairs NIS function and accordingly causes radioiodine-resistant metastasis. BRAF mediates signal transduction through the MEK-ERK pathway, however, inhibiting this pathway or inhibiting specifically RAF is not enough to induce functional NIS expression or radioiodine uptake. Currently many groups are trying to understand this mechanism to discover new drugs inhibiting BRAF and the MEK-ERK pathway, but with not too much success. This led us to explore alternative mechanisms, and we found that the TGFbeta/Smad signaling is involved in BRAF induced-NIS repression. Moreover, TGFbeta has a strong cooperative effect with MEK-ERK in BRAF-induced epithelial mesenchymal transition (EMT), migration, and invasion. We have observed that TGFbeta controls individual *vs.* cohesive thyroid cell movement which are key determinants of metastatic dissemination. Finally, although it is well established the regulatory role for microRNAs in cell cycle and proliferation of thyroid cancer, no miRNAs have yet been involved in the formation of radioiodine-resistant metastatic disease. Overall, we are paving the way to better understand the molecular genetics of thyroid cancer that will provide us new approaches for treating this disease.

DOI: 10.1530/endoabs.35.PL2

Good times, bad times: (patho)physiology of diurnal rhythms

PL3

Good times, bad times: (patho)physiology of diurnal rhythms

Gijsbertus (Bert) van der Horst
Erasmus University Medical Center, Rotterdam, The Netherlands.

Like most organisms, we have developed an internal time keeping system that drives daily rhythms in metabolism, physiology and behavior, and allows us to optimally anticipate to the momentum of the day. At the basis of circadian timekeeping lies an intracellular molecular oscillator in which a set of clock genes cyclically regulate their own expression with an approximate (circa) 24-h (dies) periodicity. The mammalian circadian system consists of a light-entrainable master clock in the neurons of the suprachiasmatic nucleus (SCN) in the brain, and light-irresponsive peripheral clocks in the cells of virtually all other tissues. As the circadian clock drives rhythmic expression of up to 10% of the active genes (thereby conferring rhythmicity to a wide range of cellular processes such as, but certainly not limited to, energy metabolism, metabolic activation of drugs, detoxification, hormone synthesis, DNA repair, and cell cycle control), it may not come as a surprise that disruption of the circadian system is associated with disease. Indeed, genetic disruption of the circadian system in rodent models by inactivation of clock genes has been found to increase tumor growth, accelerate aging, and disrupt metabolism. Moreover, our 24/7 economy requires many people to work at 'non-standard' times. Recently, epidemiological studies have revealed a relation between disturbance of our body clock by repeated shift-work and an increased risk for developing pathologies such as cancer, metabolic syndrome, and cardiovascular disease.

This presentation will address the mechanism and biological/medical importance of the circadian clock, with special emphasis on its impact on the etiology, treatment, and prevention of disease.

DOI: 10.1530/endoabs.35.PL3

Islet transplantation

PL4

Islet Transplantation Plenary 5 (Tuesday 6th May 2014)

Stephen Gough
Oxford, UK.

Attempts at restoring endogenous insulin secretion by the transplantation of human islet tissue, initially using whole pancreas transplantation, was first reported in 1966. Although there is also a long history surrounding the transplantation of isolated human islets, it was the development and subsequent publication of the Edmonton, glucocorticoid free immunospressive regimen, in 2000, that transformed the use and availability of islet cell transplantation for people with difficult to treat type 1 diabetes mellitus (T1DM). The procedure is now regularly performed in many countries, including active programmes in Europe, the USA and Canada. In the UK it is uniquely available on the NHS, for patients satisfying guidance issued by the National Institute for Health and Clinical excellence (NICE); namely people with T1DM who suffer severe, recurrent and potentially life threatening hypoglycaemia. Whilst insulin independence may be achieved, particularly in patients receiving more than one transplant, the major benefit is resolution of severe hypoglycaemia. International data now show that the percutaneous infusion of islet cells, via the transhepatic approach into the portal vein, can produce graft function rates of up to 80% at 5 years. International outcomes from almost 700 subjects also show that this is associated with $>90\%$ recipients free from severe hypoglycaemia at 5 years. Whilst islet cell transplantation has demonstrated impressive clinical outcomes, it is still restricted to a relatively select group of people with T1DM in whom the benefits surrounding the diabetes management outweigh the requirement for life-long immunosuppression. Future developments are focusing on improvements in the procedure, including reducing the immunogenic environment to which the transplanted islets are exposed, increasing the inclusion criteria into whom islets can be transplanted and further research into the impact of islet transplantation on long term diabetes related complications.

DOI: 10.1530/endoabs.35.PL4

Simultaneous treatment of menopausal symptoms and prevention of breast cancer: Is it possible?

PL5

Menopausal hormone therapy and breast cancer: evidence of promotion not causation from tumor kinetic models

Richard Santen
Univeristy of Virginia Health Sciences System, Charlottesville, Virginia, USA.

Autopsy studies report a reservoir of small, occult, and undiagnosed breast cancers in up to 15.6% of 40–80-year-old women dying from unrelated causes. Modeling of the biologic behavior of these occult tumors facilitates interpretation of the effects of hormone therapy in menopausal women. We used iterative and mathematical techniques to develop a model of occult tumor growth (OTG) whose parameters included prevalence, effective doubling time (EDT), and detection threshold. The model was validated by comparing predicted with observed incidence of breast cancer in several populations. Iterative analysis identified a 200-day EDT, 7% prevalence and 1.16 cm detection threshold as optimal parameters for our OTG model as judged by comparison with Surveillance Epidemiology and End Results (SEER) population incidence rates in the USA. We further validated the model by comparing predicted incidence rates with those observed in five separate population databases, in three long-term contralateral breast cancer detection studies, and with data from a computer-simulated tumor growth (CSTG) model. Our model strongly suggests that menopausal hormone therapy (MHT) predominantly causes existing, occult tumors to grow more rapidly (i.e. 150 rather than 200 days doubling time) and to exceed the diagnostic threshold earlier. The model also suggests that only 6% of tumors arise *de novo* during the first 5 years of MHT. From these data we conclude that occult, undiagnosed tumors are prevalent, grow slowly, and are the biologic targets of hormone therapy for menopausal women. In addition, the results suggest that breast cancer prevention with anti-estrogens or aromatase inhibitors represents early treatment of occult breast tumors and not true prevention. From these perspectives, we envision that a key approach for the future is to identify these occult tumors early, to distinguish those that are aggressive, and to initiate treatment in the appropriate tumors at an earlier stage.

DOI: 10.1530/endoabs.35.PL5

Hypothalamic inflammation – cause or consequence of obesity?

PL6

Hypothalamic inflammation: cause or consequence of obesity?

Chun-Xia Yi
Institute for Diabetes and Obesity, Helmholtz-Zentrum München, Munich, Germany.

Despite numerous educational interventions and medical efforts efforts, modern society continues to suffer from obesity and its associated metabolic diseases, such as type 2 diabetes mellitus, and these diseases show little sign of abating. The brain, and in particular the hypothalamus, continues to gain attention as an important central target for the treatment of metabolic disease. However, most of the pharmaceutical approaches directly targeting the brain largely have failed, this might be due to an incomplete understanding of hypothalamic function in control of energy metabolism. Recent studies on obesity-induced pathophysiology discovered hypothalamic inflammation-like processes that involve complex alterations of multiple physiological and cellular parameters. Hypothalamic inflammatory-like processes observed in models of diet induced metabolic diseases not only influence neurons but also glial population, the vasculature, neuronal organelles and synapses, as well as the hypothalamic ability to sense nutrients, cytokines, and hormones. A more detailed understanding of the complex interactions between cellular and intracellular players involved in diet induced hypothalamic inflammation-like processes may hold opportunities for novel ways to effectively target obesity, diabetes and their comorbidities.

DOI: 10.1530/endoabs.35.PL6

Reproduction and energy metabolism, an ancestral balance to be preserved for women's health

PL7

Abstract unavailable.

DOI: 10.1530/endoabs.35.PL7

Symposia

Endocrine changes and treatment needs in critically ill patients

S1.1

Thyroid dysfunction in critically ill patients: to treat or not to treat?

Giorgio Iervasi[1,2]
[1]CNR Institute of Clinical Physiology, Pisa, Italy; [2]G. Monasterio Foundation, Pisa, Italy.

The low-triiodothyronine (T_3) syndrome, also referred as non thyroidal illness, is a frequent finding usually associated to a wide constellation of both acute and chronic extra-thyroid critical disorders that largely differ each other in terms of aetiology, organ involvement, evolution, and clinical impact. Independently of its origin, severity and time-course, the low-T_3 syndrome has been always considered an adaptive and positive process not needing specific treatment. More recently this concept has been challenged due the emerging experimental and clinical evidences of a fundamental role of thyroid hormone as a crucial homeostatic multi-action/multi-organ factor to preserve in particular cardiovascular system and other pathophysiologically-related vital organs such as kidney and brain. The presence and relevance of a tissue hypothyroidism secondary to a low T_3 or a low T_3/T_4 state, at least in some forms of critical diseases, may likely be underestimated. A close association between low T_3 and poor prognosis in large populations of cardiac patients has been provided, and some pilot clinical studies have been reported showing a significant improvement in terms of both cardiac function and neuroendocrine balance in both acute and chronic cardiac diseases after administration of replacement doses of synthetic thyroid hormone. Multi-center large trials documenting functional and prognostic benefits of treatment are, however, lacking; also, effective end-points, timing, type and doses of hormone replacement are largely undefined. The impact of thyroid hormone-based therapy namely in post-ischemic and idiopathic heart failure, if hypothesis is proved correct, could dramatically improve both patient health care and public health costs.

DOI: 10.1530/endoabs.35.S1.1

S1.2

Adrenal (dys)function in critically ill patients

Greet Van den Berghe
Ku Leuven – Katholieke Universiteit Leuven, Leuven, Belgium.

Critical illness is hallmarked by hypercortisolemia, traditionally attributed to stress-induced hypothalamic–pituitary–adrenal axis activation. However, as low plasma ACTH concentrations and reduced responsiveness to ACTH have been reported, we hypothesized that reduced cortisol metabolism could play a major role. To systematically test this hypothesis, we recently performed six studies in matched ICU patients and healthy controls. These measured daily ACTH and cortisol plasma concentrations ($n=59$); morning plasma cortisol clearance, metabolism and production via deuterated-steroid tracer infusions ($n=20$); plasma clearance of 100 mg hydrocortisone bolus injection ($n=28$); urinary cortisol metabolites ($n=51$); mRNA and protein of major cortisol-metabolizing enzymes in liver and adipose tissue ($n=64$); and repeated (every 10 min) plasma ACTH and cortisol concentrations overnight to quantify pulsatile hormone secretion and dose-responses ($n=48$). Morning total and free plasma cortisol concentrations were consistently higher, while ACTH was lower in critically ill patients than in healthy controls. Morning cortisol production was only 83% higher than in healthy controls, and correlated positively with pro-inflammatory cytokines, not with ACTH. Patients without systemic inflammation did not have an elevated cortisol production at all despite very high plasma cortisol. In contrast, cortisol clearance during low dose tracer infusion and after 100 mg hydrocortisone was uniformly lowered to less than half the values in healthy subjects, irrespective of the inflammatory status, substantially contributing to the 3.5-fold increased plasma cortisol. Impaired cortisol clearance also correlated with lower cortisol response to ACTH injection. Reduced cortisol metabolism was due to reduced inactivation of cortisol by 5β- and 5α-reductases in liver and by 11β-HSD2 in kidney, as suggested by urinary steroid ratios, tracer kinetics and enzyme expression in liver biopsies. Reduced expression of cortisol metabolizing enzymes in liver biopsies was associated with higher plasma bile-acids and cortisol. Hypercortisolism during critical illness coincided with suppressed nocturnal pulsatile ACTH and cortisol secretion and with a normal ACTH/cortisol dose–response. In conclusion, during critical illness, reduced cortisol breakdown contributes to hypercortisolemia, and ACTH suppression. This may be important not only to increase circulating cortisol levels but also to potentiate cortisol concentrations and activity within those vital tissues that express the metabolizing enzymes. The data also suggest that 'stress-doses' of hydrocortisone (200 mg/day), advocated to replace cortisol production in critically ill patients presumed to suffer from adrenal failure, may be at three- to sixfold too high.

DOI: 10.1530/endoabs.35.S1.2

S1.3

Abstract unavailable.

DOI: 10.1530/endoabs.35.S1.3

Pituitary development – from basic research to clinical practice

S2.1

Abstract unavailable.

DOI: 10.1530/endoabs.35.S2.1

S2.2

Abstract unavailable.

DOI: 10.1530/endoabs.35.S2.2

S2.3

Management of adult patients with disorders of pituitary development

Darko Kastelan
Department of Endocrinology, University Hospital Zagreb, Zagreb, Croatia.

Pituitary development involves a number of genes encoding signaling molecules and transcription factors. Genetic mutations of any of these factors are implicated in the aetiology of congenital hypopituitarism. The phenotypes of patients with pituitary development disorders might be highly variable depending on the type and severity of deficiencies and the age of diagnosis. A diagnosis of congenital pituitary hormone deficiency must be suspected when other causes of hypopituitarism have been ruled out. Detailed clinical, biological, and radiological work-up is important in those patients. A close long-term follow-up is warranted since patients may eventually develop new hormone deficiencies as is the case in the late onset corticotroph deficiency in patients with *PROP1* gene mutations. Likewise, other anterior pituitary axis may also show progressive deterioration with time. If untreated, the main symptoms of congenital hypopituitarism are: short stature, delayed puberty, metabolic syndrome, and cognitive problems. Unlike the other causes of hypopituitarism, corticotroph deficiency in patients with congenital hypopituitarism is frequently asymptomatic. Hypopituitarism has been linked to a decreased quality of life and increased morbidity/mortality due to cardiovascular and cerebrovascular diseases particularly in patients who are not substituted with GH. Therefore, an appropriate hormone replacement is required. In general, long-term prognosis of patients with congenital hypopituitarism is equivalent to the prognosis of those without

pituitary deficiencies if treatment is started immediately after the diagnosis is established. However, a few studies demonstrated normal or prolonged lifespan in patients with congenital hypopituitarism even if the hormonal deficiencies were not adequately substituted.

DOI: 10.1530/endoabs.35.S2.3

News from thyroid hormones: central transport, energy control and oxidative stress

S3.1

Neuro-glial functional coupling in deiodination mediated thyroid hormone signaling

Balázs Gereben
Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary.

Thyroid hormone is a critical regulator of brain development, function, and metabolism. The hypothalamo-pituitary–thyroid (HPT) axis controls thyroid hormone secretion of the thyroid gland. In humans, this process generates predominantly thyroxine, a stable prohormone that cannot efficiently ligand nuclear thyroid hormone receptors prior to its activation to T_3. Since the HPT axis is not capable for rapid and tissue-specific control of thyroid hormone levels, a separate system, the deiodinase enzyme family performs this task representing a prerequisite for tight-controlled thyroid hormone action. In the brain, type 2 deiodinase catalysed glial thyroid hormone activation and type 3 deiodinase mediated neuronal thyroid hormone inactivation act in concert in order to fine-tune thyroid levels under physiological and pathophysiological conditions. The talk will present current aspects of thyroid hormone metabolism in a neuro-glial context to discuss the deiodinase-mediated control of the HPT axis and hippocampal function.

DOI: 10.1530/endoabs.35.S3.1

S3.2

Novel aspects of thyroid hormone transport in the mouse brain

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Thyroid hormone (TH) actions and metabolism are intracellular events that require the transport of TH across the plasma membrane. This process is facilitated by TH transporters of which the monocarboxylate transporter 8 (MCT8) has been most intensively analyzed. In humans, inactivating mutations in the X-linked *MCT8* gene are associated with a severe form of psychomotor retardation in combination with abnormal serum TH parameters. The clinical picture (also known as Allan–Herndon–Dudley syndrome) clearly underscores the significance of MCT8 for proper brain development as well as TH metabolism and function. In mice, however, Mct8 deficiency does not grossly affect brain development whereas the endocrine abnormalities of the patients are fully replicated.

Our studies revealed that in the mouse CNS, another TH transporter is present that can partially compensate for the absence of Mct8. Whereas Mct8 plays a prominent role in facilitating the uptake of the active hormone T_3 into the brain, the organic anion transporting peptide Oatp1c1 mediates the transport of T_4 across the blood-brain barrier. Consequently, mice deficient in both transporters (Mct8/Oatp1c1 double KO mice) exhibit a pronounced hypothyroid situation in the CNS whereas peripheral organs are in a thyrotoxic state.

Here, I will present a first phenotypic description of Mct8/Oatp1c1 double KO mice that exhibit distinct deficits in neuronal differentiation as well as pronounced locomotor deficiencies. Based on our findings we propose that Mct8/Oatp1c1 double KO mice are a novel animal model for human MCT8 deficiency and a valuable model organism to test possible therapeutic interventions.

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S3.3

Oxidative damage to macromolecules in the thyroid gland: experimental evidence

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Oxidative processes are of special significance in the thyroid gland, as they are indispensable for thyroid hormone synthesis. It is estimated that huge amount of reactive oxygen species, especially of hydrogen peroxide (H_2O_2), are formed in the thyroid under physiological conditions. Also iron, present in thyroperoxidase, is required for thyroid hormone synthesis. Both, H_2O_2 and iron, constitute substrates of the most basic reaction of oxidative stress, i.e. Fenton reaction ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {}^{\bullet}OH + OH^{-}$). Another element indispensable for thyroid hormone synthesis is iodine, concentrated in the thyroid in high amounts. This trace element is known to affect red-ox balance, revealing either spectacular antioxidative or prooxidative effects. Thus, favourable conditions for oxidative damage to macromolecules are potentially created in the thyroid, justifying the statement that the thyroid gland is an organ of 'oxidative nature'. Effective protective mechanisms, comprising antioxidative molecules and the process of compartmentalization of potentially toxic molecules, must have been developed in the thyroid to maintain the balance between generation and detoxification of free radicals. However, with additional oxidative abuse caused by exogenous or endogenous prooxidants, increased damage to macromolecules may occur, potentially contributing to different thyroid diseases, cancer included. Therefore, experimental models should be elaborated to characterise most dangerous conditions leading to enhanced oxidative damage in the thyroid and to develop effective protective tools against such conditions. Fenton reaction substrates, potassium bromate, nitrobenzene, GH, IGF1, iodine, and also depletion of antioxidative mechanisms, are among factors, which were up to now documented in experimental models to reveal proxidative and/or antioxidative effects in the thyroid gland. In turn, malignant thyroid cells are characterised by increased oxidative damage to macromolecules.

The increased oxidative damage to macromolecules in the thyroid may occur in response to different exogenous/endogenous prooxidants. The contribution of this oxidative damage to thyroid diseases, cancer included, should be considered.

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Endocrine Nurses Session 1: Craniopharyngioma

S4.1

Craniopharyngioma: challenges in the management of patients with craniopharyngioma

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Craniopharyngiomas are partly cystic embryogenic malformations of the sellar and parasellar region. With an overall incidence of 0.5–2.0 new cases/million population per year, ~30–50% of all cases represent childhood craniopharyngioma. Typical manifestations at diagnosis are some combination of headache, visual impairment, polyuria/polydypsia, growth retardation, and significant weight gain. Therapy of choice in patients with favorable tumor localization is complete resection with specific focus on maintaining functions of the optical nerve and hypothalamic–pituitary axes. In patients whose unfavorable tumor localization makes maintaining hypothalamic functionality surgically challenging, a limited resection followed by local irradiation is recommended. The overall survival rates are high (92%) but occurrences of reduced quality-of-life are also high. Hypothalamic obesity has major negative impact on quality of life during long-term follow-up. Therapeutic options for hypothalamic obesity are very limited. Recurrences after complete resection and progressions of residual tumor after incomplete resection are frequent post-surgical events. Because irradiation is efficient in preventing tumor progression, appropriate timing of post-surgical irradiation is currently under investigation in a randomized multinational trial (KRANIOPHARYNGEOM 2007), which analyzes quality of life as primary endpoint.

Radical surgical strategies especially in patients with hypothalamic involvement are not recommended due to the risk of severe sequelae. In most cases, childhood craniopharyngioma should be recognized as a chronic disease requiring constant

monitoring of the clinical and quality of life consequences in order to provide optimal care of surviving patients.

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S4.2

The role of the endocrine nurse in the long term care and treatment of patients post craniopharyngioma

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After the crisis of diagnosis and surgery for craniopharyngioma, patients and families are immediately faced with the lifetime challenge of pituitary replacement therapy. The endocrine nurse assists the patient in adapting to the regimen required for a return to normal hormonal balance and optimal health. Nurses teach the purpose of prescribed hormones, and reinforce the most effective method and scheduling of each medication; this must be individualized for each patient. Deficiencies in thyroid, cortisol, gonadotropins, ADH, and GH can occur, each with its own challenges for compliance and optimal absorption. A diagnosis of diabetes insipidus is especially challenging to patients and providers. Cortisol deficiency is also a life threatening condition, and families need to acquire complete competence with stress dosing and injections; these are skills that nurses must reinforce on a regular basis. Craniopharyngioma is highly linked to significant changes in appetite and weight gain. Nurses provide education about these risks and assistance with anticipatory lifestyle changes. While the diagnosis is uncommon, all the elements of optimal care are in the expertise of the endocrine nurse. This talk will review these pituitary challenges and also the challenges of the pediatric population.

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S4.3

Psychological aspects of living with a pituitary related condition

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There is estimated to be 60 000 people with pituitary disease in the UK. Reports have identified a number of concerns and unmet psychological needs in this patient population. Many patients with pituitary disorders remain isolated, alienated, and distressed. Research has suggested that patient distress may not be identified by healthcare professionals (HCPs), resulting in significant morbidity, additional use of primary and secondary care services, and patient dissatisfaction with care.

As an example, craniopharyngioma is associated with obesity; such a change in appearance can be difficult to accept in a society where the cultural ideal is for thin bodies and thus may be associated with the development of body image problems or self-esteem issues. In addition, the diagnosis of a tumour may be associated with traumatic stress that, if unidentified and appropriately addressed, can cause problems with treatment adherence. Patients may feel disempowered from raising such concerns with HCPs, feeling that only symptoms related to the physical disease or its medical management are issues worthy of discussion at clinic appointments. While HCPs who provide care consistent with the biomedical model may unwittingly reinforce this message.

The work to develop a pituitary distress thermometer (PDT) and instruction manual may help in providing a method to both identify and support patients' psychosocial issues. Routinely used in oncology services, a distress thermometer is a structured way for a patient, working with an HCP, to identify, discuss and resolve key concerns be they practical, emotional, physical, and/or psychological. Early results from a small scale pilot study indicate that both patients and HCPs like the PDT and find it easy to use. Crucially, completing the PDT prior to a clinic appointment was felt to help prompt patients to discuss their concerns with HCPs, including problems not conventionally viewed as 'medical'.

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Obesity Beyond BMI

S5.1

Abstract unavailable.

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S5.2

Relevance of body composition analysis

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Obesity is defined as an excess of adipose tissue of sufficient magnitude to produce adverse health consequences, and is associated with increased morbi–mortality. BMI is the most frequently used diagnostic tool in the current classification system of obesity. It has the advantage that a subject's height and weight are easy and inexpensive to measure. Overweight is defined as a BMI between 25.0 and 29.9 kg/m^2 and obesity as a BMI $\geq$30.0 kg/m^2. BMI is very useful in epidemiological studies but is only a surrogate measure of body fatness and does not provide an accurate measure of body composition. In this sense, our group has shown, in a cross-sectional analysis of more than 6000 Caucasian subjects, that 29% of the lean and 80% of overweight-classified individuals according to the BMI criteria were actually obese considering their body fat. Moreover, we found a similarly altered cardiometabolic profile in non-obese individuals according to BMI but obese based on body fat, than in those individuals obese by both BMI and body fat. Furthermore, we have shown that body fat may be more determinant than BMI and even than waist circumference in diabetes development in lean subjects classified by BMI and in males in particular. Since not in all cases physicians have access to body composition analysis we have developed a predictive equation (CUN-BAE) which correlates better than BMI with several markers of insulin resistance and inflammation, suggesting that it may be helpful in clinical practice. Finally, we provide evidence suggesting that body composition should be considered in the eligibility criteria for bariatric surgery, which are currently based on BMI and the presence of major comorbidities. In summary, the inclusion of body composition measurements is very useful and desirable for both the diagnosis and follow up of the treatment of obesity.

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S5.3

Are metabolically obese individuals are really healthy?

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Obesity belongs to the five most important health burdens in modern societies and reaches with ~20% prevalence in Germany epidemic proportions. Obesity significantly increases the risk of developing metabolic (e.g. type 2 diabetes), cardiovascular, orthopaedic, psychologic, and other disorders. Despite the well established epidemiologic relationship between obesity and these co-morbidities, there is a subgroup of metabolically healthy obese patients, which seems to be protected against metabolic and cardiovascular obesity related disorders. Compared to metabolically unhealthy or high-risk obese patients, metabolically healthy obese individuals are characterized by preserved insulin sensitivity, lower liver fat content, lower visceral fat mass, as well as normal adipose tissue function. However, are metabolically obese individuals are really healthy? Despite the absence of comorbid metabolic disorders, even metabolically healthy obese individuals may have a reduced quality of life due to a number of psychosocial factors, impaired physical fitness, osteoarthritis, chronic pain, asthma, gallbladder disease, and others. Noteworthy, metabolically healthy obese individuals do not significantly improve their obesity-associated risk for the development of type 2 diabetes and vascular diseases. Therefore, distinction between metabolically healthy from high-risk obese phenotypes will facilitate the identification of the obese person who will benefit the most from early lifestyle, pharmacological or bariatric surgery interventions. A stratified treatment

approach considering these different obesity phenotypes should be introduced into clinical management of obese patients.

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Focus on novel developments of PCOS – conclusions from the PCOS Task Force

S6.1

Abstract unavailable.

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S6.2

Diagnosis of PCOS

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Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. Based on current definitions four different phenotypes have been established by Rotterdam criteria. In 2006 the Androgen Excess Society (AES) postulated that PCOS is basicly hyperandrogenic state and the presence of clinical and/or laboratory hyperandrogenism constitutes a sine qua non for PCOS diagnosis. These criteria were further consolidated in 2009 by the AES and PCOS Society Task Force Statement. According to these criteria two conditions are necessary for diagnosis of PCOS:
1. hyperandrogenism (clinical and/or biochemical),
2. ovarian dysfunction (ovulatory dysfunction and/or polycystic ovaries).
Hirsutism is the most common clinical feature of hyperandrogenic state, affecting ~70% of PCOS patients, whereas acne and alopecia are less common with the prevalence of 15–25 and 5–50% of PCOS women respectively.
Elevated free testosterone levels are observed in about 70% of patients. The present recommendation is to measure free testosterone concentration either directly or to calculate it based on the total testosterone and SHBG. Approximately 20–30% of patients demonstrate supranormal DHEAS levels. The value of androstendione measuring is unclear, but it may slightly increase the number of hperandrogenic subjects.
Confirmation of polycystic ovaries requires either the visualisation of 12 or more follicles measuring 2–9 mm or ovarian volume $>10\ cm^3$. Morphologic ovarian alteration may be detected in more than 80% of women with PCOS, although the false positive rate is relatively high. Other features of PCOS include among other, gonadotropin abnormalities, insulin resistance, dyslipidemia and obesity.
All PCOS women should be screened for cardiovascular risk factors which can be categorized as:
– at risk PCOS women - obesity, smoking, hypertension, dyslipidemia, subclinical vascular disease, IGT, and family history of premature CVD,
– at high risk PCOS women - metabolic syndrome, T2DM, overt vascular or renal disease.

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S6.3

Focus on novel developments of PCOS: conclusions from the PCOS Task Force: treatment of PCOS

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A recent questionnaire aiming to understand which is the practice on diagnosis and management of polycystic ovary syndrome (PCOS) has been sent to all members of ESE. More than 13% of members of ESE participated in the survey. The main results were the following: i) the NIH criteria are followed by the majority of respondents; ii) obesity and type 2 diabetes were regarded as the principal long-term concerns, whereas much less concern was given to infertility; iii) the most common treatment for patients with PCOS were metformin, lifestyle modification, and oral contraceptives; iv) more direct treatments of infertility were used by $<20\%$ of the respondents. It clearly appears that endocrinologists have some different clinical perspectives when compared with gynaecologists, particularly in the treatment of choice. Treatment of PCOS by both endocrinologists and gynecologists largely depends on what they know about the pathophysiology of PCOS and on the main complains of each patient. Targeting treatment on patient's need, including a clear balance among costs, benefits, and side effects, and based on the dominant phenotype, appears to be the best strategy.

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Nontumorous pituitary diseases

S7.1

Abstract unavailable.

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S7.2

Unusual pituitary infections

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The first case of pituitary abscess was described a 100 years ago and since then, only a few 100 cases have been reported in the literature, mainly as case reports. Bacterial infections are the most common etiology, while tuberculosis, viral, fungal, and parasitic infections occur much less frequently. Pituitary infections may be primary or secondary and may develop due to hematogenous seeding or by direct extension of adjacent infections (sphenoid sinusitis, cavernous sinus thrombophlebitis, meningitis, or following tooth extraction). Risk factors for pituitary infections include immunocompromised conditions and previous pituitary surgery or irradiation. However, cases have also reported in immunocompetent patients. We will present progression of allergic fungal sinusitis (chronic inflammatory infiltrate comprised of extracellular mucin and fungal hyphae) from the sphenoid sinus to the sellar region in an immunocompetent patient. The presence of a sellar mass with suprasellar extension may be misinterpreted as pituitary macroadenoma. Endocrine symptoms may include partial or total hypopituitarism, central diabetes insipidus and hyperprolactinemia. Neurological symptoms include headache, visual disturbance, signs of meningism, cranial neuropathy and mental changes. Radiological findings of pituitary infections sometimes are difficult to distinguish from pituitary neoplasms. Due to the lack of specific clinical and radiological presentations, most patients are diagnosed only after surgery or at the time of autopsy. Hypopituitarism may develop as an acute or late consequence of pituitary infection. We will present the late sequaele of viral hypophysitis caused by Hantaan virus infection (hemorrhagic fever with renal syndrome), hypopituitarism with empty sella. In conclusion, pituitary infections should be considered in the differential diagnosis of sellar lesions and in particular as underlying pathological diagnosis of hypopituitarism.

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S7.3

Abstract unavailable.

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Membrane lipid composition and receptor function. Signalling and trafficking

S8.1

Membrane lipid composition and receptor function

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Information transfer through cellular membranes relies upon recognition of the physical and chemical information surrounding the cell by specific proteins, called receptors located in the plasma membrane (PM). These receptors are coupled to various signal relaying systems in the inter leaflet of the PM to initiate the cascade of cellular events that is characteristic of the cell and the receptor. Several receptor types alter the activity of enzymes that liberate signalling molecules originating from PM lipids and therefore, also affect the membrane lipid composition. A particularly important lipid class that plays pivotal roles in signal transduction is the phosphoinositides that not only serve as precursors of messenger molecules but also participate in recruiting and organizing protein signalling complexes on the surface of various membranes, including the PM. Moreover, increasing evidence suggest that some of the phosphoinositide changes are critical to regulate non-vesicular lipid transfer between membrane contact sites formed between various organelles. Given the small amounts of these regulatory lipids and their rapid and spatially confined changes, new approaches are required for their detection and rapid manipulation. In this presentation, we will review our most recent advances in understanding phosphoinositide dynamics and the way they contribute to the complex organization of PM receptor function and subsequent downstream signalling events. We will also discuss the principles of how these small regulatory lipids can control the overall lipid homeostasis of the cell and show examples of signal organization in specialized contact zones formed between the ER and the PM.

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S8.2

Spatiotemporal control of endocytosis

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Phosphoinositides (PIs) serve crucial roles in cell physiology ranging from cell signalling to membrane traffic. Among the seven eukaryotic PIs the best studied species is phosphatidylinositol (4,5)-bisphosphate ($PI(4,5)P_2$), which is concentrated at the plasma membrane where among many other functions it is required for the nucleation of endocytic clathrin-coated pits (CCPs). No PI other than $PI(4,5)P_2$ has been implicated in clathrin-mediated endocytosis (CME), whereas the subsequent endosomal stages of the endocytic pathway are dominated by PI 3-phosphates. How PI conversion from $PI(4,5)P_2$-positive endocytic intermediates to PI 3-phosphate (PI(3)P)-containing endosomes and, conversely, from PI(3)P-positive endosomes to plasma membrane $PI(4,5)P_2$ is achieved is unclear. In my talk I will summarize our recent findings regarding the mechanisms of PI conversion between the plasma membrane and endosomes. We recently demonstrated that formation of phosphatidylinositol-3, 4-bisphosphate ($PI(3,4)P_2$) by class II phosphatidylinositol 3-kinase C2α (PI3K C2α) spatiotemporally controls CME by regulating maturation of late-stage CCPs before fission. Timed formation of $PI(3,4)P_2$ by PI3K C2α is required for selective enrichment of the BAR domain protein SNX9 at late-stage endocytic intermediates. Combined mathematical modelling, super-resolution imaging, and genetic manipulations provide a mechanistic framework for PI conversion from $PI(4,5)P_2$ to $PI(3,4)P_2$ en route to endosomes. Furthermore, I will discuss our most recent data on the role of PI conversion in endosomal homeostasis and recycling to the plasma membrane.

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S8.3

Membrane dynamics in physiology and disease: PI3K signaling

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Phosphoinositide 3-kinase γ (PI3Kγ) is key to inflammation, allergy, cardiovascular, and metabolic disease.[1] PI3Kγ is a drug target in chronic inflammation, rheumatoid arthritis,[2] atherosclerosis[3] and allergic responses.[4,5] Localized, PI3Kγ-mediated PtdIns (3,4,5)P_3 production[5], and a distinct role of Ras selectively activating the p84–PI3Kγ-complex, can modulate PI3Kγ activation in a cell-specific way. Moreover, PI3Kγ can be controlled by upstream kinases such as protein kinase A (PKA)[6] and PKC[7], depending on target tissues. Obesity is associated with chronic, low-grade inflammation, which involves PI3Kγ-dependent leukocyte recruitment. Interestingly, PI3Kγ-null mice display attenuated high fat diet-induced obesity, fatty liver and insulin resistance. The lean PI3Kγ-null mouse phenotype can be explained by increased thermogenesis, but was found to be independent of functional PI3Kγ in the hematopoietic compartment[8]. In summary, PI3Kγ can be (re-)defined as an integrating node of G protein-coupled receptor signaling, which is also accessible to alternative input signals downstream of protein kinases. PI3Kγ responds to metabolic and inflammatory stress, and provides modes of modulation of metabolic disease, inflammation and cardiovascular disease. For reviews see[9].

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EYES Session - Cold metabolic inflammation in obesity: ignored complication and treatment target?

S9.1

Introducing EYES: European Young Endocrine Scientists

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The 'European Young Endocrine Scientists' (EYES) founded in 2011, is a committee under the patronage of the European Society of Endocinology (ESE). The primary goal of this committee is to increase the mutual exchange of ideas and knowledge between young endocrinologists – from basic researchers to clinicians – across Europe in the initial stages of their career. EYES enables young endocrinologists (<35 years) from all ESE member societies to actively contribute to all aspects of the society's activities, enabling them to fully develop into the next generation of endocrinologists. Furthermore, the committee will provide a platform for young scientists in endocrinology to make them feel welcome at ESE and to familiarize with the society's conferences. EYES assists young scientists to find a personal way through the different fields of endocrinology.

EYES aimes to support annual meetings exclusively for young scientists in different European countries (2014: Belgrade, Serbia). These meetings shall give an opportunity to young scientists to present work in progress, to improve presentation skills and to establish a scientific network in all fields of endocrinology.

In an attempt to link young endocrinologists all over Europe and to represent our special interests within the ESE, we would like to invite all interested young researchers and clinicians to take part in this exciting project.

Check out our ESE EYES homepage and interactive forum (www.ese-hormones.org/youngendo/), listen to our EYES symposium and join our social evening event during ECE 2014.

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S9.2

Fertility: PCOS: metformin

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Insulin resistance and its resultant hyperinsulinaemia seem to play a pivotal role in the pathogenesis of polycystic ovary syndrome (PCOS), which apart from its cosmetic and metabolic consequences also lead to fertility problems. Therefore, metformin – a biguanide used as the first line of pharmacotherapy in patients with type 2 diabetes mellitus (T2DM), is often prescribed to women with PCOS in order to decrease the consequences of hyperinsulinaemia and to restore ovulation. Nevertheless, the efficacy of metformin in restoring fertility in unovulatory women with PCOS remains questionable and according to the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group its routine use for this indication is not recommended. In contrary, life-style interventions including dietary treatment and the implementation of physical activity seems to be very effective in restoring fertility in obese women with PCOS, however large well controlled randomized studies are still warranted.

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S9.3

The emerging landscape for nanomedicine in atherosclerosis

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Major clinical events such as myocardial infarction and stroke are caused by atherosclerosis, a lipid-driven chronic inflammatory disease affecting the arterial wall. In recognition of the inflammatory drive in cardiovascular disease (CVD), a major interest has risen to complement current standards for high-risk patients by therapeutically targeting the inflammatory process. Prior to clinical application, therapeutic candidates are required to have a robust anti-inflammatory effect without affecting systemic immunity. Local delivery of drugs via nanomedicine offers the advantage of enhancing local drug accumulation at target sites, while decreasing systemic exposure. In fact, several nanotherapeutical formulations of anticancer and anti-inflammatory drugs have been approved for clinical use based upon their improved balance of efficacy versus toxicity. Nevertheless, the efforts to promote alternative local delivery modalities in CVD has lagged behind. Part of the reluctance in CVD pertains to the notion that the atherosclerotic lesion represents a poorly perfused compartment with low accessibility for therapeutic compounds. More recently, however, we have shown that the atherosclerotic lesions in humans can be targeted, provided that the compound has a prolonged plasma half-life allowing for sufficient time to extravasate into the atherosclerotic lesion. To evaluate the local efficacy of nanomedicinal compunds at the level of the artieral wall, several emerging non-invasive imaging modalities, including PET/CT and DCE-MRI, can serve as surrogate imaging markers in relatively small-scaled clinical trials.

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Difficulties in the treatment of Graves' orbitopathy

S10.1

New therapeutic approach in Graves' orbitopathy

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There is preliminary evidence that B cell depletion with rituximab (RTX), a chimeric mouse-human monoclonal antibody directed against the CD 20 antigen on B lymphocytes, may be effective for the treatment of moderate-severe Graves' orbitopathy (GO). While mostly non-controlled studies have shown that this modality of immunosuppression has potential in the therapy of moderate–severe GO, in particular for the control of the active, inflammatory phase of the disease. The main question, when one has to approach treatment of GO, is whether RTX may act as a disease modifying drug, when compared to i.v. methylprednisolone (IVMP) at immunosuppressive doses. Based on the limited, but promising, experience, it is reasonable to hypothesize a potential utility of RTX in the treatment of active GO, although several questions still need to be answered. What do we know about the effects of RTX in controlling the progression of inflammation in GO? What do we know about the mechanisms by which RTX counteracts tissue expansion within the inflamed orbit? Has RTX been used in randomized controlled studies? Preliminary results of one randomized trial confirm a better therapeutic outcome of RTX in active moderate–severe GO, when compared to IVMP and seem to suggest a disease modifying effect of the drug. The data reported on RTX therapy in GO suggest that B-cell depletion may be pursued shortly after diagnosis, and not only as a therapeutic option when standard immunosuppression has failed.

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S10.2

Radiotherapy in Graves' orbitopathy: current status

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Treatment of Graves' orbitopathy (GO) remains a diagnostic and therapeutic challenge for clinicians all over the world. The elimination of risk factors, like encouraging smoking cessation, achieving euthyroidism and local measures usage are the most important and usually sufficient treatment methods in most mild cases. A course of selenium may also be beneficial. High-dose i.v. glucocorticosteroids remain the first-line therapy in moderate-to-severe orbitopathy, however in some patients such treatment may be insufficient. Radiotherapy for GO have been used for decades and is considered to be effective in active GO, however less than i.v. glucocorticosteroids. It effects mainly eye motility and soft tissue changes with almost no influence on exophthalmos. The combination of these two therapies has proven to be even more effective than either treatment alone, especially in subjects with resistant or recurrent GO. Orbital radiotherapy seems to be a safe procedure with a few adverse effects observed long after therapy. It should be avoided in patients with retinopathy due to diabetes mellitus, hypertensive subjects and young subjects (under 35 years old). Orbital radiotherapy, as a safe and generally effective second-line therapy, is used in some countries as a supporting method during the second course of i.v. glucocorticosteroids, if the response for the first course is not satisfactory. However, some more randomized, double-blind studies are needed to confirm fully its clinical usefulness.

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S10.3

When should we perform orbital decompression

Anja Eckstein

Since the surgical techniques of orbital decompression have changed considerably due to endoscopic techniques, piezosurgery and navigation indication for orbital decompression have expanded. There two real emergency indications: optic nerve compression (DON) and corneal ulceration. In DON patients decompression is performed if no stable remission can be achieved after two weeks of high dose i.v. steroids. In these patients the medial wall should always be included in the surgical procedure since the prolapse of the medial rectus muscles into the ethmoidal cells provide a safe volume increase in the orbital apex. In cases of corneal ulceration decompression should be performed immediately to prevent corneal scaring and amnion membrane transplantation can be done at the same time. In cases of marked chemosis conjunctival approaches should be prevented. Another relative emergency situation is apical crowding in elder patients with concomitant glaucoma. Since the optic nerve is much more vulnerable in these patients and intraocular pressure is usually poorly controlled due to impaired venous outflow in GO, decompression will lead to significant improvement of optic nerve perfusion. The improvement of venous drainage due to decompression can help to improve therapy resistant inflammatory swelling with surgical decompression. In most of the patients a significant decrease of inflammatory swelling can be observed after decompression. In inactive disease stages decompression can be performed to reduce proptosis. Patients who have no diplopia in primary position prior surgery have to

be informed about diplopia risk due to decompression, which is high in case of medial wall decompression and low for lateral wall decompression (5–7%). Lateral wall decompression reduces the risk for the medial wall – the so called balanced decompression is the most widely applied technique with a diplopia risk of about 25%. Inferior nasal approaches have a much high risk (about 60%).

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Long term outcome of 'cured' pituitary patients

S11.1

Long-term outcome of 'cured' patients: acromegaly

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Active acromegaly is associated with considerable morbidity and increased mortality. Multimodality treatment of acromegaly is nowadays effective in the vast majority of patients and consequently survival of acromegaly has improved/normalized.

Nevertheless, significant chronic physical and psychological complaints persist in the long-term follow-up after cure of acromegaly and quality of life in patients has reported to remain significantly reduced despite biochemical cure.

The definition of biochemical cure can be subject to debate and is largely dependent on the used assay. The long-term outcome of patients with 'cured' acromegaly is described, i.e. the global health status of patients with a special focus on the most prevalent invalidating sequelae of acromegaly on the skeleton, i.e. acromegalic arthropathy and vertebral fractures. The main factors of influence of severity of joint disease and progression appears to be the severity of GH excess prior to diagnosis, but also current GH/IGFI levels and other potential modifiable factors have been suggested. Quality of life is dependent on joint disease, but also psychological factors, i.e. depression scores determine the perceived severity of joint disease.

Patient perception of disease increasingly receives attention and was recently studied with existing questionnaires, but also with qualitative health research using focus groups. Results will be discussed in the context of available quality of life studies.

In conclusion, despite biochemical cure, many patients suffer from complications of acromegaly, and an optimal care model will require a multidisciplinary approach, including physiotherapist, and psychologists.

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S11.2

Quality of life in patients with non-functioning pituitary adenomas

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Non-functioning pituitary adenomas (NFA) are associated with significant morbidity. Published data on the quality of life (QoL) of NFA patients are scarce and conflicting: some studies indicate a reduced QoL in patients with adequately treated NFAs while others demonstrate that subjective health-related QoL is not compromised to any major extent compared to the general population. Most published studies indicate specific subgroups of patients which are particularly affected, with various types of pituitary insufficiency, radiotherapy, age and gender being the factors most commonly found to have a significant measurable impact upon the QoL of treated NFA patients.

The objective of this talk is to review some of the discordant findings in the literature and to briefly present our own recent work aimed to evaluate the QoL in NFA patients followed-up in a tertiary endocrine UK referral centre.

This will hopefully help to highlight some practical measures to prevent relevant factors with a negative impact on QoL and to offer most of the NFA patients the prospect of treatment which will provide a minimally affected QoL.

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S11.3

Abstract unavailable.

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Gut microbiota in diabetes and obesity

S12.1

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S12.2

Fecal transplantation in obesity/type 2 diabetes Dr M Nieuwdorp

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Alterations in (small) intestinal microbiota are associated with obesity and insulin resistance, with the latter usually characterized by low grade endotoxemia. We recently showed that fecal transplantation (infusing intestinal microbiota from lean donors) in male recipients with metabolic syndrome has beneficial effects on the recipients' microbiota composition and glucose metabolism via lowering plasma endotoxin levels (Vrieze, Gastroenterology 2012). Moreover, preliminary data suggest that 4 weeks daily oral gavage with one of the identified small intestinal bacterial strains (butyrate producer *Eubacterium hallii*) has dose dependent beneficial effects on insulin sensitivity and liversteatosis in male *db/db* mice. Combined our data suggest that specific intestinal bacterial strains might be developed as therapeutic targets to normalize inflammatory tone and insulin sensitivity in humans.

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S12.3

Functional interactions between diet, microbiota and host: effects on intestinal architecture and host nutrient absorption

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The human gut is home to a vast number of bacteria, the microbiota, whose genomes complement our own set of genes. The gut microbiota functions at the intersection between host genotype and diet to modulate host physiology and metabolism, and recent data have revealed that an altered gut microbiota can contribute to obesity. The gut microbiota affects host physiology and metabolism by several mechanisms including increased energy harvest from the diet, modulation of lipid metabolism, altered endocrine function, and increased inflammatory tone. Furthermore, the microbiota influences intestinal epithelial and vascular architecture which in turn may affect nutrient absorption.

The composition of the microbiota is influenced by several factors including early environmental exposures and diet.
Gut microbiota contribute to host metabolic efficiency by increasing energy availability through the fermentation of dietary fiber and production of short-chain fatty acids in the colon which are proposed to stimulate secretion of the proglucagon-derived incretin hormone GLP-1. Germ-free and antibiotic-treated mice, which have severely reduced SCFA levels, have increased basal GLP-1 levels in the plasma and increased proglucagon expression specifically in the colon. Increasing energy supply suppressed colonic proglucagon expression in GF mice suggesting that colonic L-cells sense local energy availability and regulate basal GLP-1 secretion accordingly.
Increased GLP-1 levels in GF mice did not improve the incretin response but instead slowed intestinal transit suggesting that GLP-1 have additional effects on host physiology apart from the incretin effect. Increasing colon-derived GLP-1 may be an adaptive response to insufficient energy availability in the colon that slows intestinal transit and allows for greater nutrient absorption.

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Androgen excess in women and PCOS: conclusions from the PCOS Task Force

S13.1

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Clinical outcome of medical intervention in Disorder of Sex Development (DSD)

S14.1

dsd-LIFE: clinical European outcome study of disorders of sex development

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Disorders of sex development (DSD) include a conglomerate of rare conditions with discrepancy of the chromosomal, gonadal or phenotypic sex. Since the last 2 decades the genetic causes and the pathogenesis have been identified in many patients with DSD. Multidisciplinary clinical care as decision on the sex of rearing, genital surgery, hormone therapies and psychological support has a life-long impact on the affected persons. However, previous clinical outcome studies of DSD were hampered by small patient numbers, different outcome measures and conglomerates of diagnoses.
dsd-LIFE is a comprehensive clinical outcome study investigating quality of life, psychological well-being, psychosexual issues, health status, patients' views, ethical points and cultural differences in a representative number of individuals with different types of DSD. The dsd-LIFE consortium consists of 15 multidisciplinary European centers of dsd care and ethics, and collaborates closely with local support groups. Patients with the different types of 1. sex chromosome, 2. XY and 3. XX DSD will be evaluated: 1. Turner syndrome, Klinefelter syndrome, mixed gonadal dysgenesis (45,X0/46,XY); 2. testicular dysgenesis, disturbances of testosterone synthesis or action; 3. ovarian dysgenesis, congenital adrenal hyperplasia. Recruitment and evaluation of patients takes place from January 2014 to June 2016.
On basis of the received data clinical European guidelines will be developed for the different subgroups of DSD.
Moreover, dissemination of general knowledge about DSD to the public will be enhanced through the project.
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S14.2

Consequences of the preservation of underdeveloped testes in adulthood

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Disorders of sex development (DSD) is the matter of controversy on what should be the methods of treatment. One of the main problem is preservation of underdeveloped gonads. The issue of concern are especially patients with gonadal dysgenesis and Y chromosome (with presence of potential testes) (GD) and patients with androgen insensitivity (46,XY and underdeveloped testes) (AIS). It was confirmed by many studies that the risk of germ cell neoplasia (GCN) is high in these gonads, thus prepubertal gonadectomy has been recommended for years. However, the number of studied patients was relatively low, etiology of DSD was diverse, growth of gonads and their hormonal function were quite good in some cases, so resection of gonads was not obvious in every patient. Moreover, there is currently observed a growing number of protests against gonadectomy organized by adult persons with DSD who underwent such surgery in childhood.

They claim that because of gonadectomy they are deprived of fertility and convicted for the life-long hypogonadism treatment. Nevertheless, a study on adult patients with GD and AIS with preserved gonads until adulthood leads us to the conclusion that most of underdeveloped testes has poor hormonal function and need sex steroid supplementation. Only one out of 145 gonads revealed spermatogenesis advanced to spermatozoa, which gives prognosis of potential fertility. A lot of these gonads revealed overt germ cell tumours or preinvasive intratubular GCN and were removed because of it. Besides, the psychic condition was worse in persons with preserved one or both gonads in comparison to those after early gonadectomy. Further studies on the justification of underdeveloped testes preservation are still expected. Results of the dsd-LIFE European project with a large group of DSD patients may give the additional advice.

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S14.3

Developmental disruption of paracrine hormone regulation in the pathogenesis of germ cell neoplasms

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The most common testicular germ cell tumours (TGCT), seminoma or non-seminoma, occur in young adults and are derived from an intratubular precursor, carcinoma *in situ* testis (CIS). CIS cells display characteristics of developmentally arrested fetal gonocytes which during puberty acquire some features of more mature germ cells. Developing germ cells are under control of their somatic niche (Sertoli- and peri-tubular cells) and androgen-producing Leydig cells. A developmental disruption of this cross-communication, which is most pronounced in genetic disorders of sex development (DSD), leads to the maturation arrest and later neoplastic transformation of gonocytes. Among the disrupted pathways, the SRY function, the androgen signalling, and the sex-dimorphic mitosis–meiosis switch have been identified. In normally virilised men with TGCT and no overt signs of DSD, except a history of cryptorchidism, mild hypospadias and/or fertility problems, more subtle signs of gonadal dysgenesis are commonly found, consistent with a notion that testicular dysgenesis syndrome (TDS) is a milder manifestation of DSD. The aetiology of the rising incidence of TGCTs and milder TDS phenotypes remains to be elucidated, but involves predominantly environmental/lifestyle factors that target germ cell development. Modulation by genomic variation and epigenetic factors may explain the individual- and population-level differences in the prevalence of TGCT.

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Thromboembolism and contraception

S15.1

Epidemiology of sex steroid-related thromboembolism

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Venous thrombosis is a common disease, with an annual incidence of 1–4/1000 persons. Before menopause its incidence is low and strongly increases with age. Combined hormonal contraceptives (COC) increased the risk of VTE. COC use explains a substantial part of VTE among childbearing-aged women and VTE is the most important determinant of the benefit/risk profile of hormonal contraceptive. The increase in thrombotic risk is the highest the first year of COC use and third generation pill use (desogestrel or gestodène) is associated with an increased VTE risk as compared to second generation (levonorgestrel) pill use (OR: 1.7 95% CI 1.4-2.0). Specific molecules combined with ethinyl-estradiol (EE) such as drospirenone or cyproterone acetate have been now investigated. Most of the studies have reported a significant increased VTE risk among users of these COC when compared with non user or with users of second generation pill. Two new pills deliver estradiol combined with either nomegestrol acetate or dienogest. No published epidemiological data on the risk of VTE are yet available. Non oral combined contraceptives methods are also available such as the combined EEl/norelgestomin transdermal patch and the EE/etonogestrel vaginal ring. These route of EE administration seem to be more thrombogenic than second generation pill. These results are in agreement with biological data. Overall, the estrogenic climate of each contraceptive pill, depending on both EE doses and progestin molecule, could reflect the level of thrombotic risk.

Progestin-only contraceptive is an alternative for women with contraindication of estrogen use. By contrast with COC, low doses of both oral progestin contraceptives and intra-uterine levonorgestrel could be safe with respect to VTE risk.

In conclusion, newer generation formulations of hormonal contraceptives as well as the non-oral hormonal contraceptive seem to be more thrombogenic than second generation hormonal contraceptives.

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S15.2

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S15.3

The view of the gynecologist on thromboemboembolism

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Aim

Individual compliance, thrombotic risks, and relief of menstrual complains are the three main components determining hormonal contraceptive choices. The aim of this survey was to see how these terms influences choices in different age groups.

Material and methods

Literature survey.

Results

Women generally comply well with different types of hormonal contraceptives. A minority may have trouble taking one tablet a day, and others can be mood sensitive to certain progestogens.

The baseline risk of venous thrombosis increases seven times from about 1/10 000 per year at 15 years to 7/10 000 years at 49 years. Combined hormonal contraceptives increases the risk of venous thrombosis three to seven times as compared with non-users, and products with newer progestogens (desogestrel, gestodene, or drospirenone) imply about the doubled risk as compared with products with older progestogens (levonorgestrel, norethisterone, or norgestimate). Among women using high risk products for 10 years from age 30 years, more than 1% will develop a venous thrombosis. Among genetically predisposed even more. Vaginal ring and transdermal contraceptive patches belong to high risk products, while progestogen-only products do not increase the risk of venous thrombosis.

Menstrual regularity and relief of menstrual complains are wishes among many women in all ages, and combined products with all types of progestogens are generally effective in this respect.

Conclusion

Low risk combined products should be first choice in young women, while progestogen-only products including levonorgestrel intrauterine system become increasingly relevant with increasing age and with further risk factors of venous thrombosis. High risk combined products should only be used exceptionally to women who are not able to comply with low or no risk products.

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Metformin: old dog, new tricks

S16.1

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S16.2

Mechanisms of antitumoral activity of metformin in thyroid cancer

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The relative risk associated with diabetes and obesity is significantly higher for different carcinomas including thyroid cancer. There is some evidence that insulin resistance and as a consequence hyperinsulinemia rather than hyperglycemia are responsible for the higher prevalence of cancer in diabetic and obese patients. In the thyroid insulin/IGF-depending signalling is part of the mitogenic pathways that regulate benign and malignant growth. In diabetics with hyperinsulinemia metformin decreases circulating insulin levels and thereby reduces its growth-promoting effect on differentiated thyroid and thyroid cancer cells. As a thyroid-specific effect metformin lowers TSH level which is involved in the regulation of thyroid growth and is critical for the prognosis and outcome of thyroid cancer.
Beside these systemic effects, on the cellular level metformin antagonizes the growth-stimulatory effect of insulin, exerts an antimitogenic effect by inhibition of cell cycle progression and induction of apoptosis. In addition, metformin inhibits clonal cell growth of thyroid cancers cells and reduces formation of thyroid cancer spheres which are enriched with cancer stem cells. On the molecular level metformin exerts its antimitogenic effect by targeting insulin/IGF and AMPK/mTOR signalling pathways.
Remarkably, the antiproliferative effect of metformin is not restricted to differentiated thyroid cells, thyroid cancer cells and derived cancer stem cells but also operative in a doxorubicin-resistant thyroid carcinoma cell line. Metformin potentiates the antimitogenic effect of chemotherapeutic agents such as doxorubicin and cisplatin on undifferentiated thyroid carcinoma cells which allows dose reduction of these toxic drugs and in turn diminishes their side-effects. These findings suggest the well-tolerated and safe drug metformin as an adjuvant to chemotherapy of undifferentiated thyroid carcinomas which do not respond to radio-iodine treatment in diabetics and obese patients with insulin resistance and hyperinsulinemia.

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S16.3

Antitumoral effects of metformin on cancer stem cells: identification of novel molecular targets

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Epidemiological and preclinical studies propose that metformin, a first-line drug for type- 2 diabetes, exerts direct antitumoral activity. Although several clinical trials are currently ongoing, the molecular mechanisms of this effect are unknown. The AMP-activated kinase-dependent pathway, and the down-stream effectors (e.g. mTOR) are considered the main effectors. Several studies reported the involvement of, in metformin metabolic activity. Nevertheless, contrasting evidences were obtained on their role in metformin activity in tumor cells, and recently several reports showed AMPK-independent antiproliferative activity. Here we show that chloride intracellular channel 1 (CLIC1) is a direct target of metformin to block proliferation of human glioblastoma (GBM) cells, selectively interfering with cancer stem cell (CSC) subpopulation. These effects phenocopy metformin-mediated inhibition of CLIC1 chloride current, which is specifically dependent on membrane translocation and activation of this channel during the cell cycle. Metformin inhibition of CLIC1 activity, during its transient membrane insertion, arrests the transition from G1 to S phases. Furthermore, point mutation of the putative CLIC1 pore region impairs metformin interaction with CLIC1, highlighting an inhibitory activity from the extracellular side. This effect is rather specific for CSC, since no antiproliferative effects of metformin were observed on human normal stem cells. These findings highlight the role of CLIC1 as a principal target of metformin's antiproliferative activity in human CSCs, paving the way for novel and needed pharmacological approach for cancer treatment treatment.

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Cushing's syndrome

S17.1

Mortality: still increased despite cure in Cushing's disease?

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There is considerable evidence that mortality is increased in patients with Cushing's syndrome of pituitary origin. This is thought to be caused by long-term exposure to supraphysiological cortisol levels inducing harmful effects, such as hypercoagulability, insulin resistance, hypertension, bone loss, and immuno-suppression. It is assumed that some cortisol-related effects persist after treatment and the important question is whether this translates in an increased mortality in patients cured after initial therapy. Several epidemiological studies have provided data regarding this question, although individual studies are often underpowered to answer the question definitively. Quantitative summary of different studies suggests an increased mortality in Cushing's disease, even despite cure. As mortality however is clearly higher in patients not cured, the indication for treatment is not questioned by this finding. It mainly underlines that curing a disease like Cushing does not reverse long-term negative metabolic effects completely.

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S17.2

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S17.3

Medical therapy for endogenous hypercortisolism

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The initial therapy for endogenous hypercortisolism (EH) or Cushing's syndrome (CS) is almost always surgery. However, persistence or recurrence of EH is common and medical therapy may be needed to control the clinical and metabolic derangements associated with EH. Pituitary directed therapies include: Cabergoline, simple and well tolerated, cortisol (F) is normalized in 25-40% of patients but the effect is usually not enduring and Pasireotide, a somatostatin analog, reduces F in most patients with pituitary CS but normalizes F in only 25% with significant hyperglycemia in most patients. Adrenal-directed therapies include: ketoconazole which normalizes F in 50% of patients but may be associated with significant hepatotoxicity. Metyrapone, also not widely available, is often used to attenuate F secretion but there are no convincing studies showing sustained efficacy. Mitotane, adrenostatic and adrenolytic agent with significant GI/neurotoxicity, is usually reserved for patients with adrenocortical carcinoma but has also shown efficacy in other causes of EH. A new adrenostatic agent (LCI699) has also shown promise in phase II clinical trials. Etomidate, a parenterally administered hypnotic agent, is ideal for controlling EH in critically ill patients. Finally, a glucocorticoid receptor antagonist, mifepristone, has also been shown to improve clinical and metabolic consequences of EH but may cause hypokalemia, pituitary tumor enlargement, and endometrial thickening without any biochemical markers available to monitor the adequacy or inadequacy of its effect. Early detection of recurrent EH with late night salivary cortisol is important and medical, surgical, or radiotherapy should be considered long before there are any elevations of urine cortisol. The complexities and nuances of managing EH require careful individualization of therapy by an experienced endocrinologist.

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Endocrine disease during pregnancy

S18.1

Pituitary tumours during pregnancy

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The morphology and function of pituitary gland are significantly altered in pregnancy. Complex changes can be seen at the level of pituitary and target hormones, binding globulins and the effect of placental hormones are also should be taken into consideration; this makes the diagnosis of pituitary dysfunction more complicated than in the non-pregnant stage. The incidence of pituitary adenomas in child-bearing age is 0.93/100 000. All pituitary tumors carry an increased risk for tumour growth. Differential diagnosis of pituitary gland enlargement involves pituitary adenoma, pituitary or tumour apoplexy and lymphocytic hypophysitis. Hormone secretion of pituitary adenomas may influence the outcome of pregnancy and the fetus. Based on the incidence, the effect on fertility and the first line medical treatment, prolactinomas represent the most common problem during pregnancy. The risk of growth in microprolactinomas is low and the dopamine agonist therapy can be stopped safely. The probability of tumour growth is much higher in macroprolactinomas, especially with suprasellar extension. Gestation should be delayed until tumour shrinkage. Adenomas partially unresponsive to dopamine agonist treatment need transsphenoidal surgery. Regular monitoring of clinical signs and visual disturbances is required during pregnancy; symptoms of tumour expansion indicate MRI. The use of bromocriptine and cabergoline is safe; however, the exposure of the fetus to any drug should be minimized. Acromegaly is rare in pregnancy due to impaired fertility of these patients; the risk of gestational diabetes, hypertension and cardiac complications is increased. The treatment of acromegaly usually should be delayed until delivery. Octreotide can be used in pregnant patients with compressive symptoms. Cushing's disease during pregnancy results in markedly increased maternal and fetal morbidity and mortality. Metyrapone is the drug of choice for medical therapy. Decision about the surgery or medical therapy is made individually based on the severity of the disease and gestational age.

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S18.2

Pheochromocytoma/paraganglioma in pregnancy

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The occurrence of a pheochromocytoma (Pheo) or a paraganglioma (PGL) during pregnancy is extremely rare with a frequency of 0.002% of all pregnancies.
Because of the rarity of this association and the extremely variable clinical picture of Pheo/PGL, the diagnosis constitutes a real challenge for the clinicians. In fact, the differential diagnosis between Pheo/PGL and the more frequent gestational hypertension or (pre)eclampsia is very difficult. Paroxysmal or labile hypertension or hypertension in the first 20 weeks of pregnancy should alert the clinician to suspect a Pheo/PGL.
The occurrence of Pheo/PGL in pregnancy is a life-threatening event for both the fetus and the mother. If undiagnosed, fetal and maternal mortality amount to about 40-50% but can be decreased to 15 and 5% respectively by an early diagnosis and a proper treatment.
Diagnosis stems on laboratory results. The recommended test is the measurement of plasma or urinary metanephrines in view of their highest negative predictive value.
Tumor localization is performed by magnetic resonance imaging.
After diagnosis, the recommended treatment, to be continued until surgery, is with α-blockers, phenoxybenzamine or doxazosine. Surgical removal depends on the time of diagnosis. If early diagnosed, the best period for tumor removal is the second trimester. If lately diagnosed, the tumor may be removed simultaneously with caesarian section or after delivery. Laparoscopic adrenalectomy is the recommended procedure.
Because of the young age of pregnant women and the high rate of familial forms of Pheo/PGL, genetic analysis should be offered.
In view of the rarity and the complexity of this condition, pregnant women with a Pheo/PGL should be treated by a multidisciplinary team with high level of expertise in the field.

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S18.3

Congenital adrenal hyperplasia in pregnancy

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Congenital adrenal hyperplasia (CAH), with an autosomal recessive inheritance, is characterized by impaired or absent activity of one of the enzymes required for the biosynthesis of cortisol. In about 95%, CAH is due to mutations in the 21-hydroxylase gen (CYP21) and the lack of 21-hydroxylase results in a deficiency of cortisol, often also aldosterone and excess of androgens. The prenatal exposure of androgens virilise the female foetus in varying degrees depending on the level of enzyme activity, which correlates well to the mutation spectrum. CAH is clinically divided into classic CAH (SW), simple virilising CAH (SV) and non-classic (NC) disease. In classic CAH lifelong glucocorticoid and often also mineral corticoid treatment are mandatory, whereas in the NC form treatment is given when patients have symptoms such as hirsutism, oligoamenorrhoea or infertility. Patients with SW and SV have often been subjected to repeated acts of surgery correcting the virilised genitalia low pregnancy rates have been reported in women with CAH, especially the classical form. The reason for this will be discussed. All published reports include small number of pregnancies. Outcome with regard to new-born health including follow-up are usually satisfactory. There are scanty information on the progress of pregnancy and the health of the mothers. Need for change in medication during pregnancy varies. Hydrocortisone and prednisolone are the drugs of choice, dexamethasone is not recommended as this drug is passing the placenta. A majority of the women were delivered by CS. In a Swedish material of 25 pregnancies, 20% of the mothers developed gestational diabetes, significantly different compared to a matched healthy control group. An unexpected finding was the sex-ratio in the children born to CAH mothers, more girls than boys. Recommendations for the management of CAH during pregnancy will be discussed stressing the need for individualised treatment and expertise care.

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Osteoporosis - An update

S19.1

Paediatric osteoporosis

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Osteoporosis in children is not just BMD and bisphosphonates. Children are unique in their ability to grow and repair bone tissue. Diagnostics, management and the spectrum of osteoporotic conditions encountered in children are different from adults. Children can have primary osteoporosis which are rare diseases like osteogenesis imperfecta (OI), and secondary osteoporosis resulting from chronic conditions or their treatment. Disorders of the bone minerals calcium and phosphate, or their supplier vitamin D, can cause rickets and osteomalacia but are not a form of osteoporosis.

The revised ISCD paediatric position papers determine that paediatric osteoporosis is diagnosed by the combined presence of low size-corrected bone density and fractures, namely at least 1 vertebral or lower extremity long bone fracture, or at least 2 upper extremity long bone fractures. Commonly used size corrections for DXA involve calculating the volumetric density (BMAD, g/cm^3) for lumbar spine scans or removing the skull for total body scans (total body less head). Assessing musculoskeletal health overall and interpreting density results requires skill and a profound understanding of growth, bone geometry and biomechanics.

Management of paediatric osteoporosis differs according to the underlying condition, and between major treatment centres. Most experience still derives from treatment of OI, but more evidence is now emerging on secondary osteoporosis. In OI, bisphosphonate therapy can reshape broken vertebrae, increase cortical thickness and bone mass, and reduce fracture risk and pain. Questions remain on when to stop drug therapy. Apart from bisphosphonates, other new anti-resorptive drugs are now being trialled in children. Non-drug treatments such as whole body vibration therapy are also studied to assess whether muscle strengthening can influence bone.

A successful team for managing paediatric bone disorders includes physio-therapy, occupational therapy, orthopaedic surgery and expertise in DXA interpretation, and should be in the hands of a paediatrician experienced in bone disease.

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S19.2

Denosumab: current perspectives

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The interaction of RANKL with RANK is critical for the formation and function of bone-resorbing osteoclasts. Denosumab, a fully human MAB against RANKL, is an anti-resorptive drug that acts by preventing RANKL from interacting with RANK on the osteoclast precursor cells. Twice-yearly denosumab treatment is associated with markedly improved bone mineral density (BMD) and cortical and trabecular bone strength, and significantly reduced osteoporotic fracture. In clinical studies, denosumab has been shown to decrease the risk for vertebral, hip and nonvertebral fractures in women with postmenopausal osteoporosis and the risk for new vertebral fractures in men with nonmetastatic prostate cancer receiving androgen deprivation therapy, with a rate of side effects similar to placebo. Although clinical effectiveness was maintained for up to 6 months following a single injection of denosumab, cessation of treatment was associated with a more rapid reduction in BMD because the denosumab is not incorporated into the structure of the bone itself. Safety concerns include infections, skin reactions, hypocalcemia, osteonecrosis of the jaw and atypical femur fractures. Placebo-controlled and open-label extension studies showed similar adverse event (AE) and serious AE rates, relative to placebo, over up to 7 years. Data indicate that denosumab offers an effective alternative therapeutic approach for the treatment of severe osteoporosis, with positive effects on BMD and reduction of fragility fractures risk, and a potential advantage on patient adherence.

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S19.3

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New hormones and endocrine tissues

S20.1

FGF21, irisin and other novel players in endocrine metabòlic regulation

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Brown adipose tissue (BAT) activity is a relevant component of energy expenditure in mammals. Moreover, BAT constitutes an active site of glucose and lipid draining and, therefore, BAT activity is also a relevant actor in the control of glycemia and lipidemia. Recent years, possibly because of the awareness that active BAT is present in adult humans, have witnessed a burst in the identification of novel endocrine factors released by peripheral tissues that can act on BAT beyond the known sympathetic nervous system-mediated regulation. These novel factors are released by the heart (natriuretic peptides), gut (glucagon-like peptide-1, fibroblast growth factor-19) and other organs. Among them, irisin, originating in skeletal muscle, and fibroblast growth factor-21 (FGF21), mainly produced in the liver, appear especially relevant. Irisin is released mainly by muscle in response to exercise, and appears to induce preferentially the 'browning' of white adipose tissue (i.e. the appearance of brown adipocytes in white fat depots). FGF21 is mainly produced in the liver in response to fatty acid availability, but there is also evidence of FGF21 production in BAT itself in response to thermogenic stimuli, thus suggesting autocrine effects. These factors have cell-autonomous effects promoting the activity and differentiation of brown adipocytes, but indirect effects *in vivo* through modulation of sympathetic activity toward BAT cannot be excluded. The identification of novel endocrine controllers of BAT activity is of special biomedical interest as a prerequisite for developing pharmacological tools that influence BAT activity without the side effects of sympathomimetics. Moreover, some data indicate specificities in the irisin and the FGF21 endocrine systems in humans relative to current information based on rodent models. Translating emerging information to humans and validating it is essential for establishing the usefulness of novel endocrine factors in biomedical applications.

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S20.2

Products of the ghrelin gene, their role in regulating β cell and adipocyte function

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The ghrelin system comprises ghrelin, des-acyl ghrelin and obestatin, besides ghrelin receptor, GH secretagogue receptor type 1a (GHS-R1a), and the enzyme promoting ghrelin acylation, ghrelin-*O* acyl transferase (GOAT). The ghrelin peptides display different biological actions, including regulation of energy homeostasis and glucose metabolism, as well as survival and proliferative effects in different cell types. Besides the stomach, where they are mostly produced, ghrelin, des-acyl ghrelin and obestatin are expressed in the endocrine pancreas, suggesting a role in pancreas development and glucose metabolism. Indeed, ghrelin inhibits insulin secretion and insulin sensitivity, whereas des-acyl ghrelin. counteracts ghrelin inhibitory effects on insulin secretion and improves glucose metabolism. Obestatin, exerts insulinotropic effects, as well as positive actions on glucose homeostasis, likely through binding to the glucagon-like peptide 1 (GLP-1) receptor. Moreover, obestatin was recently found to promote *in vitro* β-cell generation from mouse pancreatic islet-derived precursors, indicating a major role in β-cell development. Interestingly, all the ghrelin peptides have been shown to display survival and antiapoptotic actions in pancreatic β-cells, both

in vitro and *in vivo*. The ghrelin system is also expressed in adipose tissue, and ghrelin effects have been demonstrated in both white and brown adipocytes. As for pancreatic β-cells, all the peptides exert antiapoptotic actions in white adipocytes and, whereas ghrelin is mostly diabetogenic, both des-acyl ghrelin and obestatin inhibit lipolysis and improve adipocyte function. Of note, obestatin exerts relevant effects on white adipocyte function, by positively regulating glucose homeostasis, likely through interaction with GLP-1R. Obestatin also reduces insulin resistance and prevents inflammation *in vivo*, by inhibiting pro-inflammatory cytokine release in fat, muscle and liver. Therefore, des-acyl ghrelin and obestatin may be good candidates for regenerative medicine in diabetes and may be used, in association with other compounds, for the treatment of metabolic and inflammatory disorders.

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S20.3

The gut: a key organ coordinating the brain control of energy homeostasis

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The extrinsic gastrointestinal nervous system plays a key role in the sensing of nutrients and hormones and its translation in terms of control of food intake by the CNS. Regarding major macronutrients as glucose and protein, they are sensed by the gastrointestinal neural system and the transmission of the signals to the brain promotes satiety phenomena. Glucose is sensed in the portal vein by neurons expressing the glucose receptor SGLT3 and activates the main regions of the brain involved in the control of food intake. Protein indirectly act on food intake by inducing intestinal gluconeogenesis and the sensing of released glucose by the portal glucose sensor. Similarly, soluble fibers and their products (short-chain fatty acids) mediate their anti-obesity and anti-diabetic benefits via a reflex arc with the brain inducing intestinal gluconeogenesis. At last, gut gluconeogenesis and gastrointestinal nerves may have a role in the rapid metabolic benefits of gastric bypass surgeries of obesity. This new knowledge provides novel mechanisms of control of body weight, which might be useful to envision future approaches of prevention or treatment of obesity and diabetes.

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Dilemmas in hormonal replacements

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S21.3

Dilemmas in hormonal replacements: can we offer GH replacement to patients with a history of malignancy?

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Experimental studies have shown that GH and IGFs stimulate cell mutagenesis and proliferation. Moreover, an association between high-normal serum IGF-I levels and an increased risk of malignancies has been suggested in the general population. Bearing this relationship in mind, the question raises whether patients with GH deficiency (GHD) replaced with GH are at increased risk of developing malignancies and whether some patients, particularly cancer survivors, are more prone to develop secondary cancers.

Data accumulated over a period of 30 years in more than hundred thousand GHD children showed an overall satisfactory safety profile[1] as no increase in malignancies was observed. One exception were cancer survivors, in which an increased risk of secondary brain tumours after irradiation therapy was observed when compared to patients not replaced by GH[2].

Information on cancer development in GH-replaced adults has been collected in more than twenty thousand patients over a period of 20 years. National data are available for The Netherlands[3], Sweden[4] and from two larger observational studies, Pfizer's KIMS[5] and Lilly's HypoCCS[6]. These analyses showed a comparable cancer type distribution as in the general population without an increased risk of malignancy. One study demonstrated an increased association between the development of a malignant brain tumour and irradiation therapy. A limitation of all these studies remains the short observation period to assess adequately the effect of GH replacement on cancer development, necessitating further long-term data collection.

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Novel therapies for thyroid cancer

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S22.1

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S22.2

Limits of targeted therapies and future developments

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Targeted therapies have been used for about 10 years in patients with radioactive iodine refractory differentiated thyroid cancer (DTC) or metastatic medullary thyroid cancer (MTC). Decrease in tumor volume, improvement of symptoms, increase in progression free survivals have been observed with different drugs. So far, because of trial design and because of the long survival of patients with metastatic DTC or MTC, the benefit of these drugs on overall survival has not been demonstrated. The limits of the targeted therapies are related to their safety, their efficacy, and to the absence of predictive factors for treatment efficacy.

Toxicity include cardiovascular events (hypertension, ischemic events…), asthenia, cutaneous reaction (photosensitization, folliculitis, and in some cases squamous cell cancer), diarrhea, loss of weight, and renal toxicity. They have to be taken very seriously because they can be life threatening. They are responsible of dose regimen decrease in up to 50% of the patients and drug stop in up to 25% of the patients. Prevention and early treatment of these toxicities are therefore essential to keep patients on drug as long as possible.

Despite an astonishing efficacy, treatment responses remain however insufficient with no or very few complete response observed, so far, and a limited length of response The challenges we are facing include the understanding of the mechanisms of action of the drugs and of treatment failures and the determination

of predictive factor for treatment response, including the finding of a biological significant target to choose specific targeted treatment. Drug titration should also allow a more appropriate dose regimen. In cases several drugs are available, we will need to compare treatment efficacy, treatment safety and determine the best treatment sequence. Combination of drugs is also a development to explore. Finally, a medico economic evaluation of these drugs will need to be performed. Saying so, it means that there is a long way forward to improve patient's care.

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S22.3

Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer

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Oncogenic activation of MAPK in thyroid cells leads to loss of expression of genes required for thyroid hormone biosynthesis, including the sodium iodide transporter (NIS) and thyroid peroxidase (TPO). Tumors with BRAF mutation have lower expression of NIS, explaining in part why BRAF-mutant PTCs are often resistant to RAI therapy. We developed mouse models of thyroid cancer driven by $BRAF^{V600E}$, and these tumors also lose the ability to concentrate radioiodine, which is restored by treatment with RAF or MEK inhibitors (Chakravarty D *et al*. *J Clin Invest* 2012). We conducted a 20 patient study to determine if the MAPK-kinase 1/2 (MEK 1/2) inhibitor selumetinib could reverse RAI-refractoriness in patients with metastatic thyroid cancer. Median age of the 20 evaluable patients was 61 (range 44–77) years and 11 were men. Nine patients had tumours carrying mutations of *BRAF* and 5 of *NRAS*. Selumetinib increased ^{124}I incorporation in 12/20 (4/9 BRAF; 5/5 NRAS). Eight of these 12 reached the lesional dosimetry (2000 cGy) threshold to justify RAI therapy, including all 5 NRAS cases. Of the 8 patients treated with RAI, 5 had confirmed partial responses and 3 stable disease; all patients had decreases in serum thyroglobulin (mean percent reduction of 89%). No toxicities $\geq$ grade 3 attributable to selumetinib were observed (Ho A *et al*. *N Engl J Med* 2013). These beneficial results were seen although selumetinib does not fully block MAPK signaling in thyroid cancer cells, because they relieve a feedback leading to upregulation of receptor tyrosine kinases, in particular HER3, which confers resistance to therapy (Montero-Conde C *et al*. *Cancer Discovery* 2013). New preclinical evidence from our lab now shows that combination therapies that induce a more profound and sustained inhibition of the MAPK transcriptional output in mouse models of Braf-induced thyroid cancer are associated with marked enhancement of expression of thyroid differentation markers, 124-iodine incorporation, and response to 131-iodine therapy, providing a rationale to apply these approaches to patients with high risk thyroid cancer.

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Neuroendocrine tumours

S23.1

Molecular pathogenesis of neuroendocrine tumours

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Neuroendocrine tumours (NETs) are heterogeneous neoplasm, arising from different endocrine cells distributed in many organs and tissues which share a common neuroendocrine phenotype. The neuroendocrine cells of the human body are confined to certain organs such as thyroid, pancreas or adrenals, or are dispersed throughout the body in the respiratory tract and abundantly in the intestinal mucosa. These cells belong to the diffuse endocrine cell system, which is the largest endocrine system in the body. They are able to accumulate precursor molecules in small synaptic vesicles or large dense core granules, which are then processed into hormones, peptides or amines. The hormones and amines are then released on stimulation either to the blood stream or to adjacent cells or neurons, and the release is tightly controlled. The released peptides and amines regulate various processes in the human body, such as gastrointestinal secretion, blood pressure, response to stress and regulation of local and global homeostasis in the skin. NETs present a wide spectrum of malignant diseases from rather benign to very malignant and lethal variants. They are classified according to differentiation status and tumour cell type. NETs may occur in any organ, but are mainly detected in the gastroenteropancreatic (GEP) system and in the lungs. A general and common classification has involved considerable work by the best pathologists in the world. Our current knowledge about NETs tumour biology and treatments has changed dramatically during the last decade. The main problems that clinicians and translational scientists face in overcoming these malignancies relate to various topics within molecular pathogenesis of neuroendrine tumours. My speech will hopefully highlight the importance of tumour biology, signaling transduction, genomics and biomarkers discovery in developing potential new therapeutic and diagnostic approaches to improve clinical management of NET patients.

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Nutrient regulation of metabolism and endocrine systems

S24.1

Nutrient regulation of metabolism and endocrine systems: using low-carbohydrate/high-fat diets to dissect macronutrient effects on endocrine systems

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Low-carbohydrate/high-fat diets (LC–HFD) are a popular way of dieting among the general population as several reports in humans indicate that LC–HFD induce weight loss in overweight subjects without caloric restriction and may improve glucose metabolism. However, regarding this type of diet there is also much controversy in scientific literature because clinical studies and data from animal experiments suggest severe side effects and thus warrant caution. Furthermore, the mechanism of action for weight loss remains unclear. This presentation will therefore show some of these controversial findings and the theories behind them as well as discuss success or failure of LC–HFD in humans and animal models. In addition to the use of LC–HFD for weight loss purposes, diets with such a drastic change in macronutrient composition may also be used as a research tool to investigate how nutrients regulate metabolism and endocrine systems. Another focus of this presentation will therefore be the dissection of the mechanisms which allow carbohydrates, fat and protein to exert an impact on physiology. The concept of using unique and precisely defined experimental diets in a rat model, will be introduced to demonstrate how LC–HFD with differing amounts of protein and fat affect growth, body composition, ketosis, bone metabolism, glucose metabolism and the GH/IGF-system.

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S24.2

Metabolic consequences of a high-fat diet on mouse models of GH action

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GH receptor-binding protein gene disrupted mice GHR(−/−) are dwarf, obese, insulin sensitive, and long-lived whereas GH transgenic mice are giant, glucose intolerant, lean, and short lived. When challenged with a high-fat (HF) diet, all mice became hyperinsulinemic with similar percent weight gains and increases in percent body fat and size of the epididymal, retroperitoneal, and subcutaneous fat depots. For GH mice, the increase in adipose tissue was relatively small compared with WT or GHR(−/−) mice suggesting resiliency to diet-induced obesity. Together, these results support a role for GH in energy balance regulation and nutrient partitioning.

Additionally, GH has been used previously to treat individuals with type 2 diabetes with two reports showing beneficial effects on glucose metabolism. However, concerns over GH's diabetogenic action complicate its anticipated use for these patients. Thus, preclinical animal studies could help evaluate the effects of GH for treating obesity induced type 2 diabetes. In this regard, male C57BL/6J mice were placed on a HF diet to induce obesity and type 2 diabetes. Following induction and starting at 16 weeks of age, mice were treated once daily for 6 weeks with one of four GH doses. Body weight, body composition, fasting blood glucose, insulin, glucose tolerance, liver triacylglycerol, tissue weights, and blood chemistries were determined.

Body composition measurements revealed a GH dose-dependent decrease in fat and an increase in lean mass. The subcutaneous and mesenteric fat depots were most sensitive to GH treatment. In addition, GH treatment resulted in improvement in glucose metabolism, with the highest dose normalizing glucose, glucose tolerance and liver triacylglycerol. In contrast, insulin levels were not altered by GH treatment, nor did organ weights change. However, fasting plasma leptin and resistin were significantly decreased after GH treatment. Thus**,** GH therapy improves glucose metabolism in this mouse model of obesity and type 2 diabetes.

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S24.3

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Gonadal hormones and obesity

S25.1

Gonadal hormones and obesity: estrogens and body weight

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The gonadal axis is an important modulator of both energy balance and metabolism. Estradiol administration to either ovariectomized female or male rats leads to inhibition of food intake and decreased body weight. Other studies have suggested the presence of estrous cycle variation in meal size and body weight in rodents, as well as during pregnancy and lactation. Recent data also indicate that estradiol modulates the appetite responses to central and peripheral signals and that this endocrine interaction may account for important sex differences in regulation of energy balance. The general consensus assumes that most effects of estradiol on energy homeostasis are exerted at peripheral level. However, current very evidence is changing (and challenging) our perspective about the role of estrogens on energy balance from a 'peripheral vision' to a 'central vision'. In this sense, recent data suggest that estrogen signalling in the ventromedial nucleus of the hypothalamus (VHM), specifically in steroidogenic factor -1, (SF1) neurons, plays a major role in the modulation of whole body energy homeostasis.

Here, we demonstrate that central administration of estradiol decreases the activity hypothalamic AMP-activated protein kinase (AMPK). Such induction of *de novo* lipogenesis increases activity in the sympathetic nervous system (SNS) and upregulates thermogenic markers in brown adipose tissue (BAT), leading to increased energy expenditure, and weight loss. Functional data evidence that inhibition of the lipogenic pathway in the VMH prevents CNS-mediated activation of BAT by estradiol and reverses the weight loss associated with estradiol treatment. This regulatory mechanism depends on AMPK inactivation, since genetic ablation of this enzyme in the VMH of ovariectomized rats induces feeding-independent weight loss and increased BAT thermogenesis. Overall, these findings demonstrate that estradiol-induced modulation of AMPK activity and lipid metabolism in the VMH is an important regulator of energy homeostasis.

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S25.2

PCOS and obesity: unveiling the basic links

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The polycystic ovary syndrome (PCOS), affecting 4–7% of women worldwide, is one of the most common causes of infertility. Hyperandrogenism and chronic oligo-anovulation are the prominent clinical features. However, PCOS is no longer considered as a constellation of disorders only related to the reproductive sphere, but represents an aggregation of metabolic disorders having an early onset and with advancing age predominating over reproductive disorders. Obesity, particularly the abdominal phenotype, represents the common metabolic abnormality at earlier onset in PCOS and, sometimes, it precedes the development of PCOS. The increasing prevalence of PCOS among young patients may partly depend on the exponential and epidemic increase of obesity, although long-term prospective epidemiological trials need to corroborate this hypothesis. The dominant distribution of fat in abdominal depots is known to induce profound effects on both the pathophysiology and the clinical manifestation of PCOS, by different mechanisms leading to androgen excess and increased free androgen availability and to alterations of granulosa cell function and follicle development. However, the visceral distribution of fat is unlikely to be the entire explanation for the metabolic abnormalities observed in PCOS women. It has been shown that adipose tissue of PCOS has an aberrant morphology and function. In particular, adipocytes from PCOS women are usually hypertrophic. Moreover, a local low-grade inflammation with an increased production of cytokines, chemokines, adipokines, and a decreased production of adiponectin has been described in PCOS patients. Interestingly, this chronic low-grade inflammatory state has been associated with local and systemic insulin resistance and, probably through this mechanism, to type 2 diabetes and to others cardiovascular risk factors. The crucial role of obesity in the pathogenesis and in the maintenance of PCOS is further emphasized by the efficacy of lifestyle intervention and weight loss, not only on metabolic alterations but also on hyperandrogenism and fertility.

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S25.3

Perinatal androgen exposure and body weight fate

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The etiology of PCOS is not well understood, but genetic, epigenetic, and environmental factors have all been implicated in its development. Clinical evidence suggests that excessive secretion of sex steroids, in particular androgens, plays a role in the pathophysiology of PCOS. The main metabolic phenotype is hyperinsulinemia and insulin resistance (IR). These often precede the development of type 2 diabetes mellitus (T2DM) and occur independently of body weight, although obesity worsens all symptoms. Pregnant women with PCOS tend to be obese, have increased circulating androgens, and be at increased risk of developing gestational diabetes and pre-eclampsia. They are also at risk for having either small-for-gestational-age or large-for-gestational-age infants suggesting that maternal androgen excess affects the offspring.

Animal PCOS models are needed when making the transition from scientific concepts to attaining an understanding of a human disease. A number of prenatal

androgenized animal models have been developed in rodents, sheep, and non-human primates, and their offspring develop a PCOS-like phenotype. Since most women start to develop their PCOS symptoms during early puberty, at the same time as the androgens are starting to be produced, we have developed two models in which continuous dihydrotestosterone (DHT), a nonaromatizable androgen, or letrozole, a non-steroidal inhibitor of P450 aromatase are administered from pre-pubertal age in order to study the contribution of androgens on female rats at adult age as a conceivable PCOS model. Similarities and dissimilarities with human PCOS with focus on metabolic aberrations as well as advantage and disadvantage of different rodent models will be discussed.

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Pitfalls in hormone measurement

S26.1

Guidelines on GH/IGF1 measurement

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For decades, measurements of the circulating concentrations of GH and IGF1 have constituted a mainstay in the diagnosis and clinical management of GH disorders. However, it is also well-known that considerable discrepancies exist between different assays, resulting in highly assay dependent results. Therefore, in 2009 an International Expert Committee was established with the aim to produce an international consensus statement on the standardization and evaluation of GH and IGF1 assays. The consensus was published in 2011 in *Clinical Chemistry* (57(4) 555–559) and its appearance will undoubtedly improve the accuracy and precision of the two measurements as well as provide clinically reliable and useful results.
The first part of this session summarizes the obstacles to GH and IGF1 assays and gives an overview on the content of the consensus guidelines, with special emphasis on demands to assay standardization and performance, and collection of reference values.
The consensus guidelines will improve our ability to use IGF1 as a biomarker of many diseases. However, it is important to keep in mind that the assay principle recommended to measure IGF1 only takes the presence of the IGF-binding proteins (IGFBPs) into account to a certain degree. Therefore, our laboratory has developed alternative methods to estimate the endogenous activity of the IGF-system, taking the presence of the IGFBPs into account. Specifically, we have developed a cell-based *in vitro*bioassay that enables us to compare the physiological and pathophysiological relationship between the IGFBPs, serum levels of IGF1 and the ability of the IGF-system to activate the IGF1 receptor *in vitro* (i.e. bioactive IGF).
The second part of this session presents examples of clinical situations where a discrepancy exists between the traditional IGF1 measurement and levels of bioactive IGF. This information may be helpful for clinicians when evaluating IGF1 levels in daily clinical practice.

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S26.2

Pitfalls in the measurement and interpretation of thyroid function tests

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Accurate diagnosis of thyroid dysfunction is dependent on understanding hypothalamic–pituitary–thyroid (HPT) axis physiology and the pathophysiology that can affect this classical endocrine feedback loop. Even minor perturbations of thyroid status, which may be imperceptible to the patient and clinician, can significantly alter the relationship between circulating thyroid hormone (TH) levels and pituitary TSH such is the finely-tuned nature of the axis.
Thyroid function tests (TFTs) are amongst the most commonly requested laboratory investigations in both primary and secondary care. Fortunately, most TFTs are straightforward to interpret and confirm the clinical impression of euthyroidism, hypothyroidism, or hyperthyroidism. However, in an important subgroup of patients the results of TFTs can seem confusing, either by virtue of being discordant with the clinical picture or because they appear incongruent with each other (e.g. raised TH but with non-suppressed TSH; raised TSH, but with normal TH). In such cases, it is important first to revisit the clinical context, and to consider potential confounding factors, including alterations in normal physiology (e.g. pregnancy), intercurrent (non-thyroidal) illness, and medication usage (e.g. thyroxine, amiodarone and heparin). Once these have been excluded, laboratory artefact in commonly used TSH or TH immunoassays should be screened for, thus avoiding unnecessary further investigation and/or treatment in cases where there is assay interference. In the remainder, consideration should be given to screening for rare genetic and acquired disorders of the HPT axis (e.g. resistance to thyroid hormone (RTH) and thyrotropinoma (TSHoma)).
In this session, I will discuss the main pitfalls in the measurement and interpretation of TFTs, and propose a structured algorithm for the investigation and management of patients with anomalous/discordant TFTs.

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S26.3

Advantages in the measurement of steroid hormones

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Mass spectrometry has been used to measure steroids for more than 40 years, but has gained popularity within the endocrine field in the last 15+ years. This is mainly due to technological advances that facilitated the development of high throughput methods.
Historically, steroids were measured by crude techniques such as thin layer chromatography (TLC) and later by the more sophisticated RIA. The problems with these techniques include:

i. Limited specificity where two or more steroids can be confused as they have a similar retention times.
ii. inaccurate quantitation.
iii. poor reproducibility.
iv. inability to readily identify unknown analytes.
v. low throughput methods, TLC can be extremely time-consuming as can RIA unless automated.

Mass spectrometry has allowed the endocrinologist access to a variety of techniques which produces steroid data which is specific, sensitive, quantitative, and high-throughput.
This lecture will discuss the advantages and problems of steroid analysis by mass spectrometry, focussing on two major approaches, gas chromatography/mass spectrometry (GC/MS) and liquid chromatography/tandem mass spectrometry (LC/MS–MS). GC/MS is an excellent discovery tool to explore the entirety of the steroid metabolome and several examples of the use of this method by our group will be provided. LC/MS–MS provides a high-throughput platform in addition to highly specific and sensitive determination of single steroids in the routine laboratory, and also allows for determination of groups of steroids. This will be illustrated by examples of its use in the context of adrenal and gonadal disorders.

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Brown Adipose Tissue

S27.1

White, brown, and pink adipocytes: the extraordinary plasticity of the adipose organ

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Adipocyte is a parenchymal lipid-rich cell contained into a multi-depot organ. White adipocytes store energy, brown adipocytes burns energy for thermogenesis. A third type of adipocyte appear in the adipose organ of females during pregnancy and lactation: pink adipocyte. Pink adipocytes produce and secrete milk.
The adipose organ is provided with an extraordinary plasticity because during cold exposure increase the brown component to satisfy the thermogenetic needs. When exposed to positive energy balance increase the white component to increase the storage needs. During pregnancy increase the pink component in order to satisfy the pups nutritional needs.
At cellular levels these adaptations seem to occur with a direct transformation of adult cells reprogramming their genome in order to change phenotype and function (transdifferentiation).

Understanding the underling mechanisms could help to develop new strategies to combat the metabolic syndrome (browning of the adipose organ) and the breast cancer (pinking).

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S27.3

Brown adipose tissue: the wholy grail of metabolic disease

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The activation of brown adipose tissue (BAT), the primary organ for adaptive heat production, confers beneficial effects on adiposity, insulin resistance, and hyperlipidaemia. Recent findings indicate that BAT in human adults might consist not only of classical brown adipocytes but also inducible brown adipocytes (also called beige or brite adipocytes), which are phenotypically distinct from both white and brown adipocytes. However, it remains unclear whether these beige adipocytes arising also in white adipose tissue (WAT) of mice are as powerful as their brown adipocyte relatives are.

Here we show that the conversion of white to beige adipocytes creates a cell type metabolically as powerful as classical brown adipocytes. We visualize energy catabolism in brown adipocytes in BAT as well as in beige adipocytes in inguinal WAT by non-invasive MRI and intravital imaging. Notably, only beige but not white adipocytes in WAT exhibit increased uptake of energy-rich metabolites at their access site to the capillary. The remodeling of WAT is associated with a shift in the lipidomic landscape from dietary to endogenously produced fatty acids in WAT and in plasma.

In conclusion, we provide experimental evidence that the formation and activation of beige adipocytes in WAT initiates a metabolic reprogramming of glucose and lipid metabolism, ameliorating whole body metabolic health thereby also lowering plaque burden in a humanized atherosclerosis mouse model.

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Molecular pathophysiology for clinicians: receptor-related disorders

S28.1

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S28.2

Disorders related to nuclear receptors

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Most cellular actions of the steroid and thyroid hormones, vitamins A and D, and other small lipophilic molecules are mediated through binding to nuclear receptors, which act as ligand-inducible transcription factors by recruiting coactivators and corepressors. Steroid receptors bind as homodimers to hormone-response elements (HREs) in target genes, while non-steroid receptors generally bind DNA as heterodimers with the retinoid X receptor (RXR). Our understanding of nuclear receptor actions has been significantly improved by the existence of natural mutations that cause hormone resistance syndromes. Biochemically, patients with thyroid hormone, androgen or glucocorticoid resistance have unappropriately high levels of TSH, LH, or ACTH due to lack of feedback inhibition on the hypothalamus and pituitary gland, and to reduced sensitivity of other target tissues. Several hormone resistance syndromes are inherited in an autosomal dominant manner, because the mutant receptor inhibits transcription by the WT receptor, displaying dominant negative activity. These disorders can be due to point mutations in the receptor DNA -binding domain (DBD), preventing DNA binding. Other mutations are located in the ligand-binding domain (LBD) and can disrupt dimerization or ligand binding, resulting in impaired coactivators recruitment and reduced corepressor release. In a few cases, hormone binding and dimerization are normal, but mutations occur in the carboxi-terminal AF-2 domain responsible for association with coactivators. Interestingly, we have observed that in heterodimeric receptors such as TR or VDR the presence of the RXR ligand or the interaction with non-classical coactivators such as β-catenin can partially restore transcriptional activity of AF-2 mutants. A point TR AF-2 mutant also preserves the anti-transforming and anti-tumorigenic actions of the WT receptor. The combination of cell-based studies, animal models and investigations in affected humans hopefully will help us to understand the disorders due to defects in nuclear receptors and to improve their diagnosis and management.

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S28.3

Disorders related to calcium-sensing receptor signalling

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The extracellular calcium (Ca_o^{2+})-sensing receptor (CaSR) is a family C G-protein-coupled receptor (GPCR) that regulates Ca_o^{2+} homeostasis by detecting alterations in Ca_o^{2+} concentrations and triggering $G_{q/11}$ signaling cascades, which modulate parathyroid hormone (PTH) secretion and urinary calcium excretion. Loss-of-function mutations of the CASR gene, located on chromosome 3q21.1, lead to familial hypocalciuric hypercalcaemia (FHH), which is an autosomal dominant disorder characterized by mild-to-moderate elevations of serum calcium concentrations, normal or elevated PTH concentrations, and inappropriately low urinary calcium excretion. On the other hand, gain-of-function CASR mutations result in autosomal dominant hypocalcaemia (ADH), a disorder associated with susceptibility to nephrocalcinosis and renal failure when treated with activated vitamin D preparations. *CASR* mutations are only detected in ~65% of FHH and ADH patients, and mapping studies in FHH kindreds have revealed additional loci on chromosome 19p and 19q13.3, thereby indicating genetic heterogeneity for FHH. These two genetically distinct types of FHH are designated as FHH2 and FHH3. Mutations of G-protein subunit α_{11} ($G\alpha_{11}$), encoded by *GNA11* on chromosome 19p, have recently been identified as the cause of FHH2. *In vitro* expression of FHH2-associated GNA11 mutations diminished the sensitivity of CaSR-expressing cells to Ca_o^{2+}, consistent with a loss-of-function. GNA11 mutations have also been reported to lead to a form of ADH designated 'ADH2', and these ADH2-associated GNA11 mutations induce a gain-of-function in CaSR-expressing cells. Loss-of function mutations of adaptor protein 2 sigma subunit 2 (AP2σ2), encoded by *AP2S1* on chromosome 19q13.3, have been identified as the cause for FHH3, and >20% of FHH patients who do not harbor CaSR mutations have an *AP2S1* mutation. AP2σ2 is involved in clathrin-mediated endocytosis and demonstrated to regulate CaSR cell surface expression and signal transduction. The discovery of key proteins involved in CaSR signalling and recycling has provided new insights into GPCR function and calcium homeostasis.

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S29.1

Mediterranean diet in the prevention of cardiovascular disease

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Several observational cohort studies and one secondary prevention trial (the Lyon diet study) have shown an inverse association between adherence to the Mediterranean diet and cardiovascular risk. The PREDIMED study is a multicenter, randomized, nutritional intervention trial designed to assess the effects of the Mediterranean diet (MedDiet) on incident cardiovascular diseases (CVDs), in the context of primary prevention of CVD. Participants (7447 elderly individuals at high risk of CVD) were randomized into three dietary intervention

groups: MedDiet supplemented with extra-virgin olive oil (EVOO), MedDiet supplemented with mixed nuts, and control diet (advice on a low-fat diet). After 4.8 years, 288 major CVD events occurred; hazard ratios were 0.70 (95% CI, 0.53–0.91) for the MedDiet + EVOO and 0.70 (CI, 0.53–0.94) for the MedDiet + nuts compared to the control group. Respective hazard ratios for incident diabetes (273 cases) among 3541 non-diabetic participants were 0.60 (0.43–0.85) and 0.82 (0.61–1.10) compared to the control group. In both MedDiet interventions a decreased risk of peripheral artery disease was also observed compared to the control diet. After 1 year follow-up, participants in the MedDiet + nuts group showed a significant 13.7% reduction in prevalence of metabolic syndrome, compared to reductions of 6.7 and 2.0% in the MdeDiet + EVOO and control groups, respectively. Analyses of intermediate markers of cardiovascular risk demonstrated beneficial effects of the MedDiets on blood pressure, lipid profiles, insulin resistance, and other emergent CVD risk factors such us peripheral inflammation, oxidative stress, and carotid atherosclerosis. The PREDIMED trial showed that a high-unsaturated fat and antioxidant-rich dietary pattern such as the MedDiet, supplemented with EVOO or nuts, appears to be optimal for the prevention of diabetes and cardiovascular events in elderly individuals at high cardiovascular risk.

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Meet the Expert Sessions

MTE1

Abstract unavailable.

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MTE2

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MTE3

Premature ovarian insufficiency

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Premature ovarian failure or primary ovarian insufficiency (POI) is characterized by amenorrhea occurring before the age of 40-year-old, with elevated gonadotropins (FSH >20 mIU/ml). It affects 1–2% of women. So far, in more than 75% of cases, its etiology remains unknown.

The obvious causes are chemotherapy, radiotherapy and ovarian surgery, mainly for bilateral ovarian endometriomas. Genetic causes of POI include rare diseases, such as blepharophimosis, galactosemia, Perrault syndrome, APECED syndrome (autoimmune polyendocrinopathy and candidosis ectodermal dystrophy) or most frequently Turner syndrome. Apart from 45X monosomy, or 46XX, 45X mosaicisms from Turner syndrome, other X chromosome abnormalities can be identified such as Xq deletions, X, autosome translocations and *FRAXA* premutations. In familial cases, *FRAXA* premutations are identified in 13% of cases. *SF1* (*NR5A1*) mutations are rare, $<2\%$ of cases, initially described in families including 46XY DSD patients.

In the past years, new genes have been identified thanks to animal models and powerful genetic techniques such as CGH-array, GWAS and exome sequencing. For instance, disruption of Newborn Ovary Homeobox (*Nobox*) gene induces non syndromic ovarian failure in mouse. *NOBOX* mutations have been identified in 6% of cases in a large cohort of POI patients. Furthermore, familial studies have identified regions linked to POI. Recently a mutation in stromal antigen 3 (*STAG3*) has been found in a consanguineous family. After informed consent, a karyotype should be performed as well as a search for *FRAXA* premutation. Next generation sequencing is starting to test a panel of genes within a single analysis. Hormonal replacement therapy associating estrogen and progestin is recommended in patients with POI until the age of natural menopause. POI should not be considered as premature menopause as HRT is necessary and reversibility of ovarian failure can be noticed in some cases.

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MTE4

The zebrafish, a teleost model recapitulating the mammalian molecular events during endocrine development and function

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In the last decades, the tropical teleost zebrafish (*Danio rerio*) has proved to be an excellent vertebrate system to model mammalian molecular events occurring during embryonic development, organ formation and adult physiology, either under normal or pathological conditions. Low costs and small dimensions, external fertilization and high fecundity, tissue transparency, rapid development, availability of mutant and transgenic lines, easy manipulability for gene perturbation and pharmacological screening, are some examples of the advantages characterizing this model organism.

In the past 15 years, the use of zebrafish in the endocrinology field has been mainly focused on the analysis of endocrine organ development. Our team and other research groups have elucidated the main steps leading to the formation of endocrine glands such as pancreatic islets and thyroid, hypothalamus and pituitary, interrenal gland and gonads.

Comparison of the zebrafish endocrine system to that of mammals has demonstrated that the systems are sufficiently similar for zebrafish to be employed as a model for endocrine research.

In more recent years, new zebrafish-based tools have been generated to elucidate *in vivo* the molecular cross-talks occurring among cells, tissues and organs. Signalling pathway reporter lines represent an interesting implementation of classical transgenesis to visualize *in vivo*, in an intact organism, the anatomical regions that, in a given time interval, are responding to a specific signalling pathway. To generate these transgenic fish lines, signal-specific responsive sequences, identified at the genomic level, are multimerized and placed upstream of reporter genes, typically encoding for fluorescent proteins such as GFP or mCherry. At present, a series of pathway reporter lines are already available, among which Bmp, Shh, FGF, Notch, TGFβ, Wnt, hypoxia and glucocorticoid signalling. Our group is currently generating and validating additional lines, among which the cAMP/CREB pathway, while others, such as thyroid hormone and Foxo signalling, are in the planning phase. Preliminary results and envisaged applications will be presented and discussed.

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MTE5

The Year in the Adrenals

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In this session, the most recent publications related to the topic and published in 2013/2014 will be discussed and set into a clinical and problem-oriented context. In primary aldosteronism three Nature genetics papers have elucidated the genetic basis of aldosterone-producing adenomas. In addition, an important AVS expert consensus has been published (Hypertension 2014). Also, in 2014, a revised Endocrine Society Practice Guidline for primary aldosteronism is expected (JCEM). In adrenal Cushing s syndrome three manuscripts published in the NEJM have elucidated the specific pathophysiologic mechanism of ACTH independent macronodular adrenal hyperplasia and sporadic cortisol producing adenomas. A systematic review (JCEM) has highlighted the beneficial outcome of bilateral adrenalectomy for Cushing s disease in a large series of publications. We will discuss a manuscript (JCEM) reporting the use of the monoclonal CD20 antibody rituximap to induce remission in freshly diagnosed Addison s disease. Also, a clinical study (EJE) comparing IV and sc hydrocortisone for adrenal crisis will be reported. Finally we will discuss cost effectiveness of adrenalectomy vs watchfull waiting in adrenal incidentaomas of 4 cm size and above (Surgery).

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MTE6

Abstract unavailable.

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MTE7

Therapeutic dilemmas in NETs

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During recent years, there has been some increase in the incidence of gastroenteropancreatic neuroendocrine tumours (GEP–NETs). In spite of noticeable advances in development of contemporary diagnostics and therapeutics, neuroendocrine tumours still present many clinical challenges to every-day clinical practice.
Therapeutic dilemmas will be presented as a case study including an example of a male patient JA, aged 68, diagnosed with hormone inactive pancreatic NET (NET G1) with metastases to the liver, bones and lymph nodes, who had undergone surgical removal of pancreatic cancer located in the body and tail of the pancreas, wedge resection of the right lobe of the liver, resection of the spleen (in 2000), chemotherapy and radio-frequency thermal ablation of liver metastasis. Slow progression of the volume of metastatic lesions in the liver and deterioration of clinical presentation was observed from 2004. PET/CT scans (^{68}Ga and ^{18}FDG) made in 2010 confirmed neuroendocrine tumours had spread over the body and demonstrated the presence of somatostatin receptors within some areas of the liver, bones and lymph nodes. However, because of the increased FDG uptake within many metastatic lesions observed in ^{18}FDG PET/CT, the patient was not eligible for systemic radioisotope therapy (PRRT). The patient received cold somatostatin analogues and radioembolisation of metastatic liver tumours (SIRT – intra-arterial administration of Y-90 DOTA-TATE), which led to a temporary stabilisation of symptoms. However, since further disease progression was noted, the therapy regimen was modified and supplemented with a targeted mTOR-inhibitor therapy, which improved clinical symptoms and caused partial regression of metastatic lesions in the liver and skeletal system recorded in the ^{68}Ga-DOTA-TATE PET/CT and ^{18}FDG PET/CT check-up examinations.
Conclusions
Patients with GEP–NETs constitute a very differentiated group with diverse tumour biological behavior, which causes a variety of potential therapeutic problems. Therefore, these patients require personalised treatment modalities and, in particular, co-operation between interdisciplinary teams in making therapeutic decisions in order to achieve the best possible outcome.

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MTE8

Abstract unavailable.

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MTE9

Abstract unavailable.

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MTE10

Pituitary disorders and osteoporosis

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Different hormonal disorders can influence bone metabolism and cause secondary osteoporosis. In childhood, pituitary disorders hamper gaining of proper peak bone mass and skeletal size, later on in the adult life they can increase bone loss. The consequence of diminished bone strength is significant increase of fracture risk. Among pituitary disorders such effects are possible in patients with GH, prolactin, gonadotropins secretion disturbances, and GH and ACTH excess, while hypopituitarism, hyperprolactinemia, Cushing's disease and acromegaly. In hypopituitarism, thyroid hormones and GH deficiency (GHD) cause bone metabolism disturbances and impairs skeletal growth, later on disturbances in GH and gonadotropins secretion lead to osteopenia or osteoporosis. There is an increased fracture risk in GHD patients. Sometimes, additional effect of secondary hypogonadism, hyperprolactinemia and GHD is observed while hypopituitarism due to pituitary tumor. Hyperprolactinemia increases bone resorption and BMD loss, there is increased fracture risk in patients with prolactinoma. Hypercortisolism due to Cushing's disease (ACTH-dependent Cushing's syndrome) diminishes formation and increases resorption of bone, causing trabecular bone loss and increased fracture risk. Moreover, there are decreased calcium absorption and disturbances in sex steroids secretion. In acromegaly, GH excess stimulates bone formation, but concomitant hyperpolactinemia and hypogonadism caused by pituitary macroadenoma lead to the increase of bone resorption and spinal fractures.

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MTE11

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MTE12

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MTE13

Pituitary apoplexy: diagnosis and management

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Pituitary apoplexy is an uncommon emergency. It presents often with sudden thunder clap headaches and requires multidisciplinary team involvement. This includes an experienced neurosurgeon, endocrinologist, radiologist – the pituitary multidisciplinary team.
Urgent treatment should be given often involving steroids (after a blood cortisol has been taken). Assessment includes neurological signs which if severe may merit urgent surgery.

Surgery in these circumstances is controversial but certainly if there is profound neurological sequela including third, fourth or sixth cranial nerve problems and optic nerve problems, early surgery should be recommended to decompress the neural pathways.
Ongoing studies looking to see whether urgent surgery improves neurological outcomes in borderline cases.
Patients who have had pituitary apoplexy require long-term follow-up because pituitary tumours which commonly cause this problem can recur.

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MTE14

Real-time monitoring of GPCR signalling in living cells

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G-protein coupled receptors (GPCRs) constitute the largest family of receptors and mediated the effects of many hormones and neurotransmitters. Whereas GPCRs and their signalling cascades have been intensively studied at the molecular and, more recently, structural level, many important aspects of GPCR signalling remain elusive. A major reason for this resides in the limited spatial and temporal resolution of standard biochemical methods. To overcome these limitations, we and other groups are developing methods based on fluorescence microscopy that can be used to monitor GPCR signalling directly in living cells and tissues with high spatiotemporal resolution. A first approach takes advantage of genetically encoded sensors based on the principle of fluorescence resonance energy transfer (FRET). These sensors allow monitoring all the major steps of GPCR signalling, ranging from ligand/receptor interactions to the production of soluble second messengers and the activation of downstream kinases. In order to study GPCR signalling under highly physiological conditions, transgenic animals expressing these sensors can also be generated. Such an approach was instrumental for demonstrating that GPCRs can continue signalling via classical G-protein pathways and cyclic AMP after internalization into the endosomal compartment (1,2). A more recent approach is based on single-molecule microscopy methods, which allow investigating the localization of receptors in nanodomains and their dynamic behaviour to an unprecedented level (3). The rapid advancement in this field will likely play a crucial role in the ongoing quest to unravel the intimate nature of GPCRs and their signalling cascades.
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MTE15

Abstract unavailable.

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MTE16

Postmenopausal hyperandrogenism

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Menopause is a state of relative hyperandrogenism resulting from the abrupt fall of estrogen levels due to ovarian senescence and the steady decline of androgen levels with aging. Frank hyperandrogenism, characterized by hyperandrogenemia and clinical hyperandrogenism, in postmenopausal women is most commonly the result of functional causes of hyperandrogenism, which usually pre-exist menopause from early reproductive years, and are aggravated by the physiological changes of menopause. However, less common causes of timorous hyperandrogenism should also be considered. Polycystic ovary syndrome (PCOS) is the most common cause of functional hyperandrogenism in women during reproductive years, while *de novo* diagnosis of the syndrome after menopause is problematic. Recent evidence suggest that in patients with PCOS the elevated androgen levels of both ovarian and adrenal origin persist after menopause, possibly contributing to significant long-term consequences including higher prevalence of cardiovascular disease and hormone-dependent malignancies. States of insulin resistance and relative concomitant hyperinsulinemia (such as obesity and diabetes mellitus type 2) are frequent in women after menopause, while it is well documented that aberrations of carbohydrate metabolism parameters are associated to hyperandrogenism. Pre-existing steroidogenic deficiencies (most commonly 21-hydroxylase deficiency) may exacerbate hyperandrogenism after menopause and usually present with mild symptomatology. Although relatively rare androgen-secreting neoplasms originating from either the adrenals or the ovaries are potentionally life-threatening causes of androgen excess, while a subset occur more frequently in postmenopausal women. Androgen-producing tumors usually present with abrupt symptoms of hyperandrogenism or even virilization. Other causes of hyperandrogenism after menopause include relatively rare and common endocrinopathies such as Cushing's syndrome, acromegaly and thyroid disorders as well as the use of specific drugs. The combination of a detailed history, proper clinical assessment and appropriate laboratory and imaging evaluation is required for the accurate differential diagnosis, proper clinical management and prevention of the long-term sequelae of hyperandrogenism after menopause and particularly identify the less common but potentially life threatening disorders.

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MTE17

FGF23 and phosphorus homeostasis: physiology and pathophysiology

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The great majority of the phosphorus in the body is found as phosphate (PO_4). Phosphate is critical for the maintenance of bone and skeletal integrity, is a necessary component of important biomolecules, such as RNA and DNA, and is central to signal transduction and cell metabolism. The appropriate serum phosphate concentration is maintained based on the endocrine communication between the skeleton, the kidney, and the intestine. The classical view of phosphate regulation is based on the actions of vitamin D and parathyroid hormone. However, nowadays the fibroblast growth factor (FGF) 23/Klotho axis is recognized as a critical biological system in the regulation of phosphate homeostasis. FGF23 functions as a phosphaturic hormone and also as a counter-regulatory hormone of $1,25(OH)_2D_3$. FGF23 is secreted from the bone and acts on the kidney to suppress phosphate reabsorption and $1,25(OH)_2D_3$ synthesis, thereby inducing a negative phosphate balance. A critical feature of FGF23 is that it requires Klotho, a single-pass transmembrane protein, as a co-receptor. Klotho protein forms constitutive binary complexes with the fibroblast growth factor receptors (FGFRs) and increases their binding affinity to and selectivity for FGF23. Without Klotho, FGF23 cannot bind to and activate its cognate FGFRs at physiological concentrations. In addition, there is a soluble form of Klotho with humoral actions. Beyond this physiological role, growing evidence suggest that the FGF23/Klotho system has relevant pathophysiological implications in different clinical processes, including renal phosphate wasting syndromes, chronic kidney disease, secondary hyperparathyroidism, as well as vascular dysfunction, atherosclerosis and cardiovascular morbidity and mortality. Therefore, the components of this new biological system may have great interest as clinical biomarkers, as well as therapeutic targets in these pathological conditions.

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Oral communications

Thyroid clinical

OC1.1

Esophagus motility in overt hypothyroidism

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Introduction
Gastrointestinal tract is one of the most affected systems in hypothyroidism. The most plausible mechanism in the pathogenesis is the development of interstitial edema subsequent to accumulation of glycosaminoglycans. Despite decreased esophageal emptying, prolonged esophageal and gastric transit time has been indicated in previous reports, the mechanism of thyroid hormones activity on the gastrointestinal system is not yet fully understood. To our knowledge, this is the first prospective study conducted to evaluate esophagus motility by manometry in hypothyroid patients.
Methods
The study enrolled with 28 overt, newly diagnosed hypothyroid patients and 29 age-sex matched healthy controls. Twenty-one females and 7 males (mean age: 46.9 years, range 23–76 years) with overt hypothyroidism and 22 females and 7 males (mean age: 45.0 years, range 19–77 years) with healthy control subjects were recruited to study. Esophageal manometry was performed using MMS (Medical Measurement Systems bv. The Netherlands) Solar GI - Air Charged Intelligent Gastrointestinal Conventional Manometry.
Results
In manometric measurements, LESP (lower esophageal sphincter pressure) was 19.5 ± 6.5 mmHg in hypothyroid patients and 17.48 ± 4.65 mmHg in controls and there was no significant difference ($P = 0.18$). Percentage of relaxation was 61.5% and 80.9% and it was significantly lower in hypothyroid patients than controls ($P < 0.001$). Additionally, duration of relaxation was found 3.85 ± 2.3 and 5.5 ± 2.28 s in patients and controls, respectively ($P = 0.009$). In patient group, LESP was positively correlated with fT3 ($P = 0.033$) and the duration of the contraction was negatively correlated with fT4 ($P = 0.044$).
Conclusion
In this study we observed that hypothyroid state can affect esophagus motility via shortened duration of relaxation and reduced percentage of relaxation. Hypothyroid patients should be questioned and explored for esophageal symptoms. Further studies are needed to clarify the effect of thyroid hormones and thyroid antibodies on esophagus motility.

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OC1.2

Levothyroxine substitution in subclinical hypothyroidism: Does it have a beneficial effect on all-cause mortality?

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Background
Subclinical hypothyroidism is associated with a number of cardiovascular risk factors such as hypertension, hypercholesterolemia, and diastolic dysfunction, but only limited data exist on long-term outcome of levothyroxine substitution therapy.
Objectives
To examine effects of levothyroxine substitution treatment on mortality in patients with subclinical hypothyroidism.
Study design
Historical cohort study.
Methods
Patients >18 years consulting their general practitioner from 2000–2009 in Copenhagen, Denmark, who underwent thyroid blood tests, were identified by individual-level linkage of nationwide registries. Only patients with subclinical hypothyroidism at baseline were included (defined as elevated TSH with normal free T4). History of thyroid disease, related medication or treatment with lithium, amiodarone, and glucocorticoids were excluded. Levothyroxine treatment was only considered if initiated within 6 months from baseline. Incidence rate ratios (IRR) of all-cause mortality were analyzed using Poisson regression models.
Results
The total cohort comprised 628 953 patients of whom 12 212 (1.9%) had subclinical hypothyroidism (mean age 55.2 (S.D. ±18.8) years; 79.8% female). Within the first 6 months, 2452 patients (20.1%) were prescribed with levothyroxine. The remaining 9760 patients (79.9%) either initiated levothyroxine therapy later than 6 months after their initial blood test or otherwise did not receive any substitution treatment at all. During a mean follow-up time of 5.0 (S.D. ±2.6) years 1566 patients died. Overall mortality rate was 26/1000 person-years (py) and 21/1000 (py) among untreated and levothyroxine treated respectively. No benefit on all-cause mortality was found in patients substituted with levothyroxine (IRR 1.02 (95% CI: 0.88–1.17)).
Conclusion
In patients with subclinical hypothyroidism substitution with levothyroxine is not associated with lower all-cause mortality.

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OC1.3

Chronic liothyronine (T3) treatment in stable heart failure patients with low T3 syndrome: A randomised, double-blind, cross-over, placebo-controlled intervention study (The LIHFA study)

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Background and aim
Low T3 syndrome is associated with a poor prognosis in patients with chronic heart failure (CHF). It is controversial whether T3 treatment is indicated in CHF. A previous study using intravenous infusion of T3 for 72 h suggested a beneficial effect on cardiac performance.
We aimed to evaluate the effect of 13 weeks of T3 treatment in patients with stable CHF on left ventricular ejection fraction (LVEF) compared to placebo.
Material and methods
Oral T3 (median (interquartile range (IQR))) 20 (16.7–35) mg/day vs placebo was given for 13 weeks. T3 dose was regulated by repeated TSH measurements, in order not to render patients hyperthyroid. Inclusion: baseline serumT3 levels ≤1.6 nmol/l, LVEF <45 by echocardiography, fully up-titrated with regard to CHF medicine. LVEF was measured as 3D MultiGAated Acquisition (MUGA) at baseline (week 0), cross-over (week 13) and end of study (week 26).
We included 13 patients (11 men), mean age 73.9 years (6.8 years), serum T3 (median (IQR)) 1.4 nmol/l (1.2–1.4 nmol/l) and LVEF of 43% (40–48%).
Results (median (IQR))
Treatment did not change LVEF compared to placebo (ΔLVEF −1.9% (2.0% (−1.1-6.4%) vs −1.9% (−4.28–7.1%) $P = 0.33$)). LVEF after treatment was not significantly improved compared to LVEF after placebo (46.1% (42.8–51.7%) vs 44.1% (37.4–49.0%) $P = 0.38$). Changes in LVEF from baseline to 13 weeks of treatment were not associated with neither serum T3 baseline level ($r = 0.29$, $P = 0.32$) nor baseline LVEF ($r = -0.01$, $P = 0.82$). Heart rate did not change either and no new arrhythmias were recorded.
Conclusion
√Liothyronin treatment in 13 weeks did not change systolic function in CHF patients with low T3 syndrome.

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OC1.4

Consequences of experimental hyperthyroidism on brain structure and function in humans

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Objective
Disturbed levels of thyroid hormones are associated with neuropsychiatric disorders, including memory impairments. Even short-term hyperthyroidism may affect properties of the human brain. To investigate the influence of thyroid hormones, we conducted functional neuroimaging. The aim of this study was to evaluate functional changes in working memory performance.
Materials and Methods
Twenty healthy, male, right-handed subjects (age range 21–49 years, median 30 years) in good general health without mood or cognitive disorders and normal thyroid state gave their informed consent to participate. High resolution 3D T1-weighted MRI scans were acquired by 3T MRI from the subjects before and after taking 250 µg L-thyroxin for a period of 8 weeks. Thyroid function was measured and subjectively assessed by questionnaire. For both time points all participants conducted a working memory task (*n*-back task). Functional analysis was performed using Statistical Parametric Mapping 8 (SPM8).
Results
Despite a lack of significant subjective changes assessed by questionnaire all subjects developed biochemical hyperthyroidism after 8 weeks with a 1.7-fold increase in baseline fT3, a 2.1-fold increase in fT4 levels and suppressed TSH levels. In the hyperthyroid condition the subjects showed slower reaction times, but a higher accuracy in 0-back memory tasks. The more difficult the memory tasks were, the less effect could be seen. Significant differences of task-induced functional activation were found especially in bilateral insulae, bilateral prefrontal cortex, bilateral anterior cingulate cortex and bilateral posteriocerebellum ($P<0.05$, FWE corrected). When comparing euthyroid and hyperthyroid condition in relation to task-induced activation, differences of activation were found in the right prefrontal cortex, as well as in the right parahippocampal area ($P<0.001$, uncorrected).
Conclusion
It can be concluded that a short-term intake of thyroid hormones lead to an activation of brain areas associated with working memory.

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OC1.5

rh-TSH (Thyrogen) aided radioiodine therapy in children and adolescents with DTC

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Background
Although recombinant human TSH (rhTSH) is widely used to aid radioiodine treatment of differentiated thyroid cancer (DTC), however, there are data on its effectivness in children and adolescents with DTC.
The aim of our retrospective study was to evaluate effectiveness and safety of rhTSH aided radioiodine treatment in DTC patients 18 years of age or younger.
Material and Methods
Fifty five children/adolescents (median age 15 years, range 4–18 years) with the diagnosis of DTC were treated using the approved adult rh-TSH regimen (on 0.9 mg i.m. injection daily on 2 consecutive days) and therapeutic activity of ^{131}I (median 3.7 GBq, range 2.2–3.8 GBq). Thyroglobulin was evaluated on 1st and 6 of stimulation, and whole body scan (WBS) on day 6th. Patients were followed-up on 6 months interval. The median follow up after the treatment is 43 months.
Results
Peak TSH concentration post-rhTSH exceeded 25 mU/l in all children. In all children the peak stimulated thyroglobulin was achieved on day 6 of stimulation (median 4 ng/ml, range 0.17-1080).
In children treated with radioiodine as an adjunct to total thyroidectomy ($n=45$), in 8(17%) second radioiodine treatment was performed due to persistent radioiodine uptake in thyroid bed and or elevated thyroglobulin concentration. There was one (2%) structural recurrence in thyroid bed during subsequent follow-up.
In ten patients (22%) distant metastases to lung/mediastinum were diagnosed. In all morphological (radiological or scintigraphic) remission was achieved, but in none thyroglobulin decreased below detection level during last 131-I therapy.
None side effects were observed after rh-TSH application.
Conclusions
rhTSH aided radioiodine treatment in children/adolescents with DTC is a safe and effective treatment. It allows to avoid hypothyroidism during L-thyroxine withdrawal without any significant side effects. The first results suggest that the treatment is effective both as an adjuvant and radical treatment but longer follow up is necessary.

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Adrenal clinical

OC2.1

Armadillo repeat containing 5 gene (ARMC5) alterations in a large cohort of 98 ACTH-independant macronodular adrenal hyperplasia (AIMAH) patients: genotype/phenotype correlations.

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Introduction
ACTH-independent macronodular adrenal hyperplasia (AIMAH) is often an incidental finding, but may be diagnosed in patients with Cushing's syndrome. We have recently identified germline mutations in the armadillo repeat containing 5 gene (*ARMC5*) in AIMAH patients, associated with somatic second hits specific of each AIMAH nodule (Assié et al, NEJM, 2013). The aim is to characterize the prevalence of ARMC5 mutations in AIMAH patients and the genotype/phenotype correlations.
Methods
Ninety-eight unrelated patients with AIMAH, defined as a bilateral adrenal enlargement of at least 1 cm, were included. *ARMC5* was sequenced by SANGER. Wild type and mutated patients were compared using Student *t*-tests or Fisher exact tests.).
Results
ARMC5 alterations were found in 24 patients (26%). These alterations included four nonsense mutations, six missense mutations, four frameshift mutations, one inframe small deletion (discarding four aminoacids) and one microdeletion of 1.5 Mb. For four extra-patients, the leukocyte DNA was not available, but two alterations were found in the AIMAH nodule that could be sequenced. Among these four patients, two combined a nonsense mutation and a frameshift mutation, one combined a missense and a frameshift, and one an inframe deletion (one aminoacid) and a missense. None of these mutations were found in public DNA variation databases (dbSNP or 1000 genomes). All the missense mutations were predicted as probably damaging using Polyphen. *ARMC5* mutated patients were diagnosed at younger age (49 vs 55, $P=0.046$). They showed a more severe Cushing syndrome, with higher plasma cortisol after DXM 1 mg (18 vs 9 µg/dl, $P<0.001$) and a lower ACTH ($P=0.003$). They also showed bigger adrenals (107 vs 50°g of total adrenal, $P=0.001$), with more nodules than the non mutated patients ($P<0.001$). Hypertension was more frequent in the mutated patients group (95% vs 63%, $P=0.009$). ARMC5 mutated patients were more frequently operated (83% vs 33%, $P=0.001$).
Conclusion
ARMC5 mutations define a subtype of adrenal hyperplasia characterized by larger adrenals containing multiple nodules, and more prone to overt Cushing's syndrome.

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OC2.2

Constitutive activation of PRKACA in adrenal Cushing's syndrome

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Background and Methods
Corticotropin-independent Cushing's syndrome is caused by tumors or hyperplasia of the adrenal cortex. The molecular pathogenesis of cortisol producing adrenal adenomas is not well understood. Therefore, exome sequencing was performed in 10 cortisol-producing adenomas and recurrent mutations in candidate genes were evaluated in additional 171 patients with adrenocortical tumors. In addition, genome-wide copy number analysis was performed in 35 patients with cortisol-secreting bilateral hyperplasias. The effects of these genetic defects were studied both clinically and *in vitro*.
Results
Exome sequencing revealed somatic mutations in the PRKACA gene, which encodes the main catalytic subunit of cyclic AMP-dependent protein kinase (PKA), in eight of ten adenomas (c.617A>C in seven and c.595_596insCAC in one). Overall, PRKACA somatic mutations were identified in a total of 22 of 59 adenomas (37%) from patients with overt Cushing's syndrome while these mutations were not detectable in patients with subclinical hypercortisolism ($n=40$) or in other adrenal tumors ($n=82$). Among 35 patients with cortisol-producing hyperplasias, 5 (two of whom were first-degree relatives) carried a germline copy number gain of the chromosome 19 region including the PRKACA gene. *In vitro* studies demonstrated impaired inhibition of both PKA catalytic subunit mutants by the PKA regulatory subunit, while cells from patients with germline chromosomal gains showed increased protein levels of the PKA catalytic subunit; in both instances, basal PKA activity was increased.
Conclusions
Taken together this report links genetic alterations of the main catalytic subunit of PKA to human disease: germline duplications of this gene cause bilateral adrenal hyperplasias, whereas somatic PRKACA mutations lead to unilateral cortisol-producing adrenal adenomas. This is consistent with the known role of the cAMP signaling pathway in adrenal lesions associated with Cushing's syndrome.

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OC2.3

Prognostic value of DNA methylation in adrenocortical carcinomas: an ENSAT study

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Background
The prognosis of adrenocortical carcinomas (ACCs) is heterogeneous. Genome-wide methylation analysis of tumor DNA identified a sub-group of ACCs from the French COMETE network with CpG island hypermethylation evoking a CpG island methylator phenotype (CIMP). These ACCs are associated with a poorer prognosis (Barreau, JCEM 2013).
The aim was to validate the prognostic value of CIMP in a large multicentric independent cohort from ENSAT (European Network for the Study of Adrenal Tumors).
Experimental design
The CpG island methylation was measured for 27 genes by methylation-specific multiplex-ligation-dependent probe amplification (MS-MLPA) using the ME002-B1 kit (MRC-Holland, Amsterdam). The best discrimination rule and thresholds were determined on the set of 50 ACCs previously studied by pangenomic methylation. The methylation was then measured on a validation cohort of 149 ACCs from 21 centers, using the same MS-MLPA kit. Survival was analyzed using Cox models.
Results
The best classifier for the CIMP was the mean methylation of 4 MS-MLPA probes (PAX5, GSTP1, PYCARD, PAX6), with a threshold of 12% of methylation.
In the validation cohort, the sex ratio (F/M) was 1.9. The median age was 49 years. Sixty-seven percent had hormonal hypersecretion. Fifty-eight percent were localized (ENSAT stages I–II) and 42% were locally advanced or metastatic (stages III–IV). The median follow-up was 37 months.
The methylation level based on the 4-probes classifier was 21.6% (0 to 96%), comparable to the initial cohort (24.5%, $P=0.51$).
Hypermethylation was associated with decreased overall survival (HR=2.19 (1.28–3.76), $P=0.0035$) and event-free survival (HR=2.89 (1.82–4.57), $P<10–5$). The prognostic value of methylation on overall survival was independent of tumor extension (HR=2.02, $P=0.011$).
Conclusion
Tumor methylation measurement by MS-MLPA could provide a simple molecular tool for predicting the prognosis of ACCs.

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OC2.4

Detection of pheochromocytoma by enzyme immunoassay measurements of plasma metanephrines requires appropriately established upper cut-offs of reference intervals

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Aim
To determine diagnostic performance of normetanephrine (NMN) and metanephrine (MN) measured by an enzyme immunoassay (EIA) compared with liquid chromatographic–tandem mass spectrometry (LC-MS/MS).
Methods
Subjects included 341 patients (174 males) with a mean age of 52 year (range 13–86) tested for PHEO, which was confirmed in 54 patients. Samples where collected from fasting patients after 30 min of supine rest and analyzed for NMN, MN and methoxytyramine (MTY) by LC-MS/MS at Dresden and for NMN and MN by immunoassay at Nordhorn.

Results
Areas under ROC curves for the EIA (0.993) were similar to those for LC-MS/MS, with and without MTY (0.999 and 0.985), indicating excellent diagnostic performance of both methods. However, upper cutoffs (UC) stipulated by the manufacturers for the EIA (180 pg/ml for NMN and 90 pg/ml for MN) are too high to reliably identify patients with PHEO under any condition of blood sampling (26.3% patients with PHEO missed due to false negatives). Using age-adjusted UC for NMN and a static UC for MN,[1] LC-MS/MS measurements returned a diagnostic sensitivity of 98.1% with a specificity of 99.7%; sensitivity increased to 100% upon inclusion of MTY with minimal loss of specificity (99.3%). Plasma concentrations of NMN and MN were measured 44% and 26% lower by the EIA than by LC-MS/MS. Correction of UCs for that difference ($UC_{NMN} = 0.0002169 \times (age^3) + 56.5$ and $UC_{MN} = 65$ pg/m) increased diagnostic sensitivity for the EIA from 73.6% to 96.2% with a minimal loss in specificity (98.9% to 97.2%).
Conclusions
With the EIA, PHEOs can be diagnosed with high sensitivity and specificity, but UCs must be established for supine and fasting sampling conditions. Additionally, the assay needs recalibration to avoid underestimation of plasma metanephrines.
Reference
1 Eisenhofer G. et al. *Annals of Clinical Biochemistry* 50, 62–69 (2013).
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OC2.5

Treatment strategy and outcome with primary aldosteronism: a nationwide longitudinal cohort based study
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Objectives
Along with better recognition of the role of primary aldosteronism (PA) in increasing cardiovascular risk and the potential of targeted therapy for PA, the long-term mortality according to different treatments are poorly understood.
Methods
We investigated PA patients using the validated algorithms between 1999 and 2011. Their data were extracted from the whole claims of the Taiwan National Health Insurance. We used Cox regression with time-varying covariates to adjust for subsequent adrenalectomy, mineralocorticoid receptor antagonist (MRA) and potassium prescription after diagnosis.
Results
Among the 3362 PA patients who were identified, 846 patients received adrenalectomy and 452 patients expired. The incidence rate of death was 23.4 per 1000 person-years during a mean follow-up of 5.75 years. In time varying Cox model, patients who received adrenalectomy were associated with decreased risk of mortality (hazard ratio (HR) 0.32), independent of the effects of potassium supplement (HR 2.39), and age (HR, 1.09). Patients who received MRA after diagnosis did not relate to mortality risk. An additional analysis was conducted to show the defined daily dose (DDD) of MRA between 0.2 and 1.3 has the lowest impact on mortality.
Conclusion
In national wide population claim data, we provide the first time that PA patients with adrenalectomy could improve long-term risk of death, while MRA did only within appropriate prescription. The result suggests that early diagnosis and target therapy may warrant PA patients care. The findings made in the present association study need to be confirmed by randomized controlled trials to prove the observed beneficial effect of adrenalectomy on PA mortality.
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Neuroendocrinology & Signalling

OC3.1

Constant intravenous infusion of kisspeptin-54 restores LH pulsatility in women with hypothalamic amenorrhoea
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Background
Women with hypothalamic amenorrhoea (HA) have reduced LH pulsatility causing amenorrhea and infertility. Estrogen supplementation provides symptomatic relief for women with HA, but does not restore the pulsatile pattern of LH secretion which necessary for fertility. Kisspeptin-54 is a recently identified hormone, which potently stimulates GNRH secretion within the hypothalamus. The effect of exogenous kisspeptin-54 administration on LH pulsatility in women with HA is not known.
Methods
A single-blinded, placebo-controlled study was performed. Five participants with HA each attended six study visits. Participants received a continuous intravenous infusion of vehicle or kisspeptin-54 (doses 0.01, 0.03, 0.1, 0.3 or 1 nmol/kg per h) for 8 h. Blood was sampled at 10 min intervals for measurement of LH. Pulse analysis was determined by a blinded deconvolution method.
Results
As expected, LH pulsatility was minimal in HA patients during vehicle administration. As previously observed, kisspeptin-54 increased basal LH secretion dose-dependently. However kisspeptin-54 also increased pulsatile LH secretion, up to 5-fold during 0.10 nmol/kg per h infusion (mean pulsatile LH in IU/l: 7.0 ± 4.3, vehicle; 37.9 ± 17.7, kisspeptin-54; $P < 0.05$ vs vehicle). Peak numbers of LH pulses were observed at different doses of kisspeptin-54 in each participant. The mean peak number of pulses during infusion of kisspeptin-54 was 3-fold higher when compared with vehicle (number of LH pulses per 8 h: 1.6 ± 0.4, vehicle; 5.0 ± 0.5, most effective dose of kisspeptin-54, $P < 0.01$ vs vehicle). The mean secretory mass during kisspeptin-54 was also threefold higher when compared with vehicle (LH pulse secretory mass in IU/l: 3.92 ± 2.31, vehicle; 23.44 ± 12.59, most effective dose of kisspeptin-54; $P < 0.05$ vs vehicle).
Discussion
This data determines for the first time the therapeutic dose-range of kisspeptin administration associated with stimulation of pulsatile LH secretion in the treatment of infertility in women with HA. This finding has important therapeutic implications for the restoration of fertility in women with HA.
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OC3.2

Copeptin in the diagnosis and differential diagnosis of diabetes dnsipidus – the 'CoSIP-study'
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Introduction
The correct differential diagnosis of the disorders related to polyuria–polydipsia syndrome (PPS) is mandatory since inadequate treatment may lead to serious complications. The diagnostic gold standard is the water deprivation test (WDT) with direct or indirect measurement of plasma vasopressin (AVP). But test interpretation is problematic, and direct measurement of AVP is hampered by methodological difficulties. The aim of this study was to evaluate the diagnostic accuracy of copeptin in the differential diagnosis of DI.
Methods
In a prospective multicenter study, patients with a history of PPS and indication for a WDT were consecutively included. The WDT started at 0800 h with a baseline blood and urine sampling and was terminated once S-Na+ levels increased > 147 mmol/l. If this cutoff was not reached by fluid deprivation alone, a 3% saline infusion was administered. Serum samples were obtained hourly for measurement of copeptin and AVP.
Results
We present results of the first 52 patients with full data available: 13 with complete, 12 with partial central DI, 17 with PP, and 10 with nephrogenic DI. Twenty-nine were women, 23 were men. Mean (S.D.) age was 45 (16) years. Baseline copeptin levels ranged from 21–117 pmol/L in patients with nephrogenic DI, from 0.7–5.1 pmol/Llin patients with central DI (complete: 0.7–4.1 pmol/l; partial: 0.8–5.1 pmol/l) and from 0.9–13.5 pmol/l in patients with

primary polydipsia. Without prior thirsting, a single baseline copeptin level of >20 pmol/l perfectly differentiated nephrogenic DI from all other etiologies with a sensitivity and specificity of 100%, rendering a WDT unnecessary. Furthermore, a delta copeptin increase under osmotic stimulation of <2 pmol/l differentiated patients with central DI from patients with primary polydipsia with a specificity of 95.8%, a sensitivity of 94.1% and a positive likelihood ratio of 22.6.

Conclusion

Copeptin is a promising new tool in the complex diagnosis of polyuria–polydipsia syndrome

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OC3.3

Evidence for interaction between the β_2-adrenergic and the insulin receptor

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Functional interplay between different classes of receptors has emerged as a notable factor of cellular response in health and disease. One of the most prominent examples of cross-talk involves the regulation of glucose metabolism, a major regulatory function under the influence of both insulin receptor (IR) and β_2-adrenergic receptor (β_2-AR) representing the receptor tyrosine kinases (RTKs) and the seven transmembrane receptors (7TMRs) respectively. The cross-talk between these different classes of receptors may occur at the RTK/7TMR level or *via* various intracellular effector/adaptor molecules such as β-arrestins. First we employed BRET^2 proximity assays to detect possible heterodimerization between β_2-AR and IR in live HEK-293 cells. BRET^2 saturation assay results suggested a constitutive IR and β_2-AR homodimerization as well as heterodimerization between the IR and β_2-AR. The existence of heterodimerization was further tested by BRET^2 competition assay, where unexpectedly, a transient increase in the BRET signal was observed when untagged β_2-AR was coexpressed with a constant amount of tagged IR suggesting that these complexes possibly constitute of trimmers or higher oligomers. Further BRET evidence for the IR/β_2-AR heterodimerization was provided by the receptor-heteromer investigation technology (HIT) showing isoproterenol- but not insulin-induced GFP^2-β-arr2 recruitment to the heteromer complex consisting of IR-Rluc8 and untagged β_2-AR; IR/β-arr2 interaction was only found to be constitutive. Next we applied informational spectrum method (ISM), a virtual spectroscopy method for investigation of protein-protein interactions. Computational peptide scanning of the β_2-AR and IR identified domains encompassing residues at the end of 7th TM domain and C-terminal tail of β_2-AR and cytoplasmic part of IR beta chain as prospective interaction domains. In summary our data suggest direct interaction between β_2-AR and IR and existence of multiprotein complexes consisting of IR, β_2-AR and β-arr2.

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OC3.4

Role Of thyroid hormone receptor β expression in lymphangiogenesis in breast carcinoma

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Lymphangiogenesis is a very important event in breast cancer development and VEGF-C and D factors play an essential role in this process. Tumoral invasion of lymphatic vessels facilitates metastasis formation and is a bad pronostic marker in this pathology. Although the thyroid hormone receptors (TRs) are ubiquitously expressed in normal tissues, inactivation and mutations of the TRβ gene are usual events in breast cancer, suggesting that the native receptors could act as tumor suppressors. Indeed, we have shown that expression of TRβ in breast cancer cells reduces tumor growth, invasion and metastasis development in nude mice. Now, we have examined a possible role of TRβ as an inhibitor of lymphangiogenesis using the highly metastatic cell line MDA-MB-468 (MDA). We observed lower levels of VEGF-C and VEGF-D mRNA in MDA cells stably expressing TRβ (MDA-TRβ) than in parental cells, and the treatment with the thyroid hormone T3 further reduced these levels. In transient transfection assays TRβ expression and T3 treatment decreased the activity of the VEGF-C promoter, showing that the receptor represses VEGF-C transcription. As expected, VEGF-C and D transcripts were lower in tumors originated by the inoculation of MDA-TRβ cells in nude mice than in those formed by parental cells. Furthermore, the expression of the lymphatic marker Lyve1 demonstrated a lower number of vessels in tumors originated by the MDA-TRβ cells. The expression of VEGF-C and D, as well as the number of lymphatic vessels, was however higher in tumors grown in hypothyroid nude mice, in accordance with previous our results showing that host hypothyroidism increases invasion and metastasis development by breast cancer cells.

These results demonstrate that TRβ reduces lymphangiogenesis, repressing VEGF-C and VEGF-D gene expression, and this repression could explain, at least in part, the actions of this receptor as a suppressor of metastatic growth.

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OC3.5

NTRK3 receptor expression is strictly associated with medullary thyroid cancer RET mutation status

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Aim of the study

Medullary thyroid cancer (MTC) occurs as hereditary and sporadic form. Hereditary type is a consequence of *RET* proto-oncogene germline mutations also somatic *RET* mutations are detectable in sporadic MTC tumors. There is a significant relation between site of mutation and the cancer phenotype as well as a clinical course of the MEN 2 Syndrome as a consequence of the different transforming potential of the *RET* gene mutations. The aim of study was to evaluate whether the differences in gene expression profile are related to the particular *RET* mutation

Methods

Fresh-frozen tumor samples from 34 MEN 2 patients and 21 *RET* negative MTC patients were collected. Germline mutation screening was performed according to standard algorithm, assumed analysis of exon 10, 11, 13, 14, 15 and 16. *RET* somatic mutations were analyzed among sporadic MTC patients and 21 exons of *RET* gene were sequenced. Gene expression profile were analyzed by using Gene Chip 1.0 ST Arrays (Affymetrix). Unsupervised analysis was carried out by hierarchical clustering. Selection of probe sets were performed using Welch t-test with FDR.

Results

Hierarchical clustering did not show any global differences in gene expression profile between type of *RET* mutation, however, supervised analysis revealed 10 genes differentially expressed between tumor samples with mutation at *RET* codon 634 and 918 of the *RET* gene. The most significant was *NTRK*3 gene. Samples with mutation at codon 918 were characterized with higher level of expression of *NTRK*3 gene. Also *NTRK*1 and *NTRK*2 were verified in our data, however, there were no significant changes observed between type of *RET* gene mutations.

Conclusions

In conclusion, RET mutation status was more significant for the overall transcriptome profile than the heredity aspect and *NTRK*3 gene showed the most distinct changes in expression between tumors with specific type of *RET* gene mutations.

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Diabetes and Obesity 1

OC4.1

The lower postprandial glucose oxidation in nondiabetic carriers of risk variants of TCF7L2 gene

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Introduction
The transcription factor 7-like 2 gene (TCF7L2) has the strongest effect on the risk of type 2 diabetes but the mechanism for this is not fully understood. Some genetic variants are associated with pancreatic B-cell function and some single nucleotide polymorphisms show a significant correlation with obesity. The aim of the study was to analyze whether TCF7L2 variants may influence body weight and body fat content, as well as postprandial glucose metabolism in non-diabetic subjects.
Description of methods/design
We genotyped previously identified TCF7L2 SNPs: rs7901695, rs7903146 and rs4506565 in 944 subjects (329 normal-weight, 337 overweight, 278 obese) who underwent anthropometric measurements, body composition analysis and OGTT. In randomly selected 59 healthy subjects standardized high-carbohydrate meal tests were performed and postprandial carbohydrate oxidation by indirect calorimetry were evaluated. Kruskal–Wallis non-parametric analysis to evaluate difference between the studied parameters was performed.
Results
In spite of the lack of differences in BMI and body fat content between studied TCF7L2 variants, subjects with CC genotype (rs7901695) presented significantly lower carbohydrate oxidation from 60 min after meal intake and significantly lower area under the curve (AUC) for glucose oxidation ($P=0.005$) in postprandial state in comparison to those with other genotypes. Significantly lower glucose oxidation, as well as lower AUC for glucose oxidation ($P=0.04$) were observed also in the carriers of TT (rs7903146) vs CC and CT genotypes.
Conclusion
Our study suggests that the TCF7L2 variants are associated with the regulation of postprandial glucose oxidation. If our results are confirmed, TCF7L2 gene-related personalized diet with lower carbohydrate content may be considered for T2DM prevention.

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OC4.2

Vildagliptin alone, and in half-dose combination with metformin, attenuates streptozotocin-induced diabetic nephropathy in high-fat fed heminephrectomized rats

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Background
Presently, a great deal of attention is being paid to investigation of pleiotropic effects of oral antidiabetic drugs. Several recent animal studies have suggested that vildagliptin and metformin could play some positive role in preventing the evolvement of diabetic nephropathy.
Aim
This pilot study, concerned with high-fat fed heminephrectomized streptozotocin (STZ)-induced diabetic rats, aimed to evaluate and compare the effects of metformin, vildagliptin and their combination on kidney histopathology and routine renal function markers.
Methods
Three weeks following unilateral nephrectomy male Wistar rats were fed with either a normal diet (non-diabetic (ND) rats) or high-fat diet for 5 weeks. Diabetes in high-fat fed rats was induced by two-time intraperitoneal administration of STZ (30 mg/kg). 9 weeks later, rats in diabetic group were divided into three subgroups to receive metformin (300 mg/kg per day in drinking water (M)), vildagliptin (8 mg/kg per day in drinking water (V)), half-dose combination (vildagliptin 4 mg/kg per day + metformin 150 mg/kg perday (V+M)), or placebo (P) for another 8 weeks, $n=5$ each.
Results
Glycated haemoglobin (%) didn't differ between diabetic treated groups (M= 11.1 ± 0.28, V= 10.7 ± 0.26, V+M= 10.7 ± 0.28, $P\geq0.05$ each; P= 12.8 ± 0.35, $P<0.05$ each),and was markedly higher compared with ND (4.7 ± 0.15, $P<0.01$ each). Although all antihyperglycaemic compounds ameliorated serum creatinine (umol/l) level (M= 93.8 ± 6.7, V= 84.7 ± 2.9, V+M= 79.4 ± 5.8; $P=103.1\pm3.7$, $P<0.05$ each), however, only vildagliptin monotherapy and combined treatment were able to considerably improve creatinine clearance (V= 2.69 ± 0.16 ml/min/kg; V+M= 3.4 ± 0.18; $P=1.7\pm0.11$, $P<0.05$ each), and reduce urinary albumin excretion ratio (V= 10.5 ± 1.07 mg/24 h, V+M= 6.7 ± 0.47; $P=26.9\pm2.0$, $P<0.01$ each). Moreover, nephroprotection in V and V+M groups was also associated with restoring morphological changes in kidney tissue.
Conclusion
We determined that vildagliptin alone, and in half-dose combination with metformin might attenuate diabetic nephropathy, in addition to hypoglycemic action. Furthermore, half-dose combined V+M treatment was more effective for this prevention.

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OC4.3

Importance of neuropeptide Y as a predictor of nephropathy in type 2 diabetic patients

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Background and aims
Neuropeptide Y (NPY) cause decrease glomerular filtration rate, aldosterone concentration, and plasma renin activity by stimulating NPY receptors in the kidney. Previous studies have suggested that NPY polymorphism is related to development of advanced diabetic nephropathy (DN). The aim of this study was to evaluate the relationship between the serum neuropeptide Y levels and different stages of DN in patients with type 2 diabetes mellitus (T2DM).
Materials and Methods
Seventy-five T2DM patients were divided into two groups according to estimated glomerular filtration rate (eGFR by MDRD (Modification of Diet in Renal Disease)): 16 cases with moderate and severe renal dysfunction (Ccr <60 ml/min/1.73 m^2) were included in group A and 59 cases with mild to normal renal function (Ccr >60 ml/min/1.73 m^2) in group B. Serum fasting glucose, HbA1c levels, high-sensitvity C-reactive protein (hsCRP), lipid profile, urinary microalbumin excretion, serum NPY, and eGFR were determined and BMI was calculated. We measured serum NPY (ELISA, BioAspect®) in fasting blood in the morning. The groups were matched by gender and duration of diabetes.
Results
NPY level was significantly higher in group A than group B ($P<0.05$). NPY levels (Geom.mean (95% CI), pg/ml) were 19.08 (5.7–58.02) and 15.14 (1.32–32.01) in group A and B respectively. Baseline characteristics of both groups will be presented. Urinary microalbuminuria levels (Geom.mean (95%CI), mg/day) were 21.6 (9.5–172.5) and 22.1 (8–150.4) in both groups respectively, and wasn't significantly different ($P=0.539$). NPY was inversely associated with the eGFR by MDRD (Spearman rho $=-0.27$, $P=0.015$), and positively correlated with diabetes duration (rho $=0.26$, $P=0.022$) and HDL (rho $=0.339$, $P=0.004$). There was no correlation between NPY and urinary microalbumin excretion ($P=0.653$). Although triglyceride level was high in group B, there was no correlation between triglyceride and NPY.
Conclusion
NPY and eGFR were negatively correlated, so NPY may be important predictor of advanced DN independent of presence of microalbuminuria. Also increased NPY level in moderate to severe renal dysfunction group may be the underlying pathogenetic factor in T2DM.

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OC4.4

Endothelial progenitor Cells exhibit decreased function but increased numbers in overt type 2 diabetic nephropathy

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Background
Endothelial progenitor cells (EPCs) play an important role in neovascularization and endothelial regeneration, and the number and function of circulating EPCs is decreased in patients with diabetic retinopathy and type 1 diabetic nephropathy. However, the number and function of EPCs in patients with type 2 diabetes nephropathy is unknown.
Methods
Participants were divided into three groups: 1) type 2 diabetes with overt nephropathy (DN group, $n=21$), 2) type 2 diabetes without micro-albuminuria (diabetes group, $n=19$), and healthy controls ($n=16$). Circulating CD34+ /vascular endothelial growth factor receptor 2 (VEGFR2)+ cells were isolated from the peripheral blood and analyzed by flow cytometry. Migration, tube formation, and apoptosis were assessed in EPCs in vitro. bcl-2/bax genes were evaluated by RT-PCR.
Results
The number of EPCs in the DN group was higher than that in the diabetes group, while the numbers of EPCs in both the DN and diabetes groups were lower than that in the control group (8.74 ± 0.24, 6.15 ± 0.30, $19.79\pm0.35\times106$/l, $P<0.05$). However, EPC function was decreased in the DN group ($P<0.05$) in both migration and tube-forming assays. The rate of apoptosis was highest in the diabetes group and lowest in the control group ($18.2\%\pm0.24\%$ vs $6.8\%\pm0.19\%$ respectively). mRNA level of bcl-2/bax was lowest in the diabetes group and highest in the DN group ($P<0.05$).
Conclusions
In type 2 diabetic nephropathy patients, EPCs' function was decreased but the number was increased compared with that in diabetes. At the same time, apoptosis of EPC in over DN stage was increased as well as the bax/bcl-2 mRNA level. Our results demonstrated that EPCs were involved in the progression of overt diabetic nephropathy and may be a predictor of disease.

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OC4.5

A comparison of lipoprotein associated phospholipase A2 and high sensitive C-reactive protein levels between diabetic and non-diabetic patients with coronary artery disease

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Background
Lipoprotein-associated phospholipase A2 (LpPLA2) is known as an emerging marker of coronary artery disease (CAD). However its role and levels have not been documented clearly in diabetic patients with CAD in Indians. The aim of this study was to explore the association of LpplA2 levels between diabetic and non-diabetic patients with CAD and compare it with other established markers like hs-CRP.
Methods
Sixty individuals with angiographically proven CAD and 30 healthy individuals matched for age & sex were studied. CAD patients were divided into two groups based on presence ($n=30$) (Group I) and absence ($n=30$) (group II) of type 2 diabetes mellitus (DM). The serum levels of LpPLA2, hs-CRP were measured by ELISA. Angiographic clinical vessel scoring was also done for all the patients.
Results
Both groups of CAD with and without DM had significantly higher levels of LpPLA2 (Group I-408.48 ± 38.96 ng/ml, Group II 272.88 ± 34.21 ng/ml respectively) and hsCRP (Group I-10.61 ± 1.34 mg/l, Group II-5.75 ± 2.59 mg/l respectively) when compared with healthy control subjects (LpPLA2 $=200.82\pm$ 20.97 ng/ml & hsCRP $=1.89\pm1.34$ mg/l) ($P<0.001$). LpplA2 levels between the two CAD groups were highly significant ($P<0.001$), levels being maximum for CAD with type 2 diabetes (Group I) which could be due an increase in its substrate sLDL and oxidised LDL in DM. Angiographic clinical vessel score of CAD severity was also higher in CAD with DM. LpPLA2 levels correlated strongly ($r=0.763$, $P<0.001$) with the angiographic clinical vessel score in diabetes patients with CAD while hsCRP has moderate correlation with the veesel score ($r=0.475$, $P<0.01$).
Conclusion
LpPLA2 and hsCRP elevation is increased with patients of type 2 diabetes mellitus with CAD as compared to only CAD patients. Measurement of LpPLA2 may be considered as a marker for better prediction of cardiovascular risk in diabetes patients.

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Adrenal & Thyroid

OC5.1

Diagnostic and therapeutic outcome in ERCUSYN: Preliminary report in over 1000 patients

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The European Registry on Cushing's Syndrome (ERCUSYN) is designed to collect prospective and follow-up data on patients with Cushing's syndrome (CS) and currently (Sep 2013) includes 1006 patients (804 F, 202 M; mean age (+s.d.) 44.7 ± 13.3 years) from 57 centers in 28 countries.
Six hundred and sixty one (66%) had pituitary-dependent CS (PIT-CS), 242 (24%) adrenal-dependent CS (ADR-CS), and 103 (10%) CS from other etiologies, including ectopic (ECT-CS). Death occurred in 35 patients (3%), 43% in PIT-CS and 31% in ECT-CS. Urinary free cortisol (UFC) supported the correct diagnosis in 92% PIT-CS, 86% ADR-CS and 100% ECT-CS. Overnight 1 mg dexamethasone suppression test (1 mg DST) reliably identified 87% PIT-CS, 90% ADR-CS, and 96% ECT-CS. Late night salivary cortisol was diagnostic in 92% PIT-CS, 87% ADR-CS, and 93% ECT-CS. Medical treatment was the first therapeutic option in 286 patients, the majority having PIT-CS (74%). Surgery was the first-line treatment in 624 patients, 399 with PIT-CS (64%), 185 with ADR-CS (30%) and 40 with other etiologies (6%). Of 553 PIT-CS patients who underwent transsphenoidal surgery, 376 (68%) experienced short-term remission (within 2 weeks of surgery), whereas 81 (15%) were not cured. Immediate clinical improvement was only observed in 19/95 (20%) patients with normal post-operative cortisol, and did not occur in a subset of 14 of 351 (4%) with postoperative hypocortisolism. Bilateral adrenalectomy was performed in 6%, 38% with ECT-CS. Long-term remission was described in 84% of PIT-CS with available data (mean follow-up, $43+38$ months), 87% of ADR-CS (after $34+28$ months), and 50% of ECT-CS (after $43+27$ months).
After a mean follow-up of 3.5 years >80% of PIT-CS and ADR-CS in ERCUSYN are in long term remission, but only 50% of ECT-CS. ERCUSYN provides an extensive overview of currently used diagnostic and therapeutic procedures in CS at EU level.

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OC5.2

Relationship between final height and cardiometabolic risk and quality of life in adults with congenital adrenal hyperplasia: United Kingdom Congenital adrenal Hyperplasia Adult Study Executive (CaHASE)

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Background
Treatment of CAH in childhood focuses on growth and development; however the impact of final height (FH) on adult health is not known. We examined the relationship between FH, adiposity, cardiometabolic risk and quality of life (QoL) in a cohort of adult patients.
Methods
Cross-sectional analysis of 199 adults with CAH. FH, waist circumference (WC) and QoL were expressed as *z*-scores adjusted for mid-parental target height (FH_{TH}) or UK population (FH_{UK} and WC_{UK}).
Results
FH correlated inversely with age (men $r=-0.38$; women $r=-0.26$, $P<0.01$). Men and women had FH_{TH} *z*-scores -2 and -1 respectively, and both groups had FH_{UK} *z*-scores -1 below the UK population ($P<0.01$). In women, FH was shorter in non-SW than SW classic CAH ($P<0.05$) and in moderately affected genotype group B women than either more severely affected groups Null and A ($P<0.01$) or mildest group C ($P<0.001$). Classic CAH patients diagnosed late were shorter than those diagnosed in the first year of life ($P<0.05$). The shortest CAH patients were 3.4 times (95% CI: 1.4 to 8.0, $P=0.006$) more likely to have hypertension than the tallest. FH did not associate with insulin sensitivity, lipid profile, adiposity and QoL. CAH patients had WC_{UK} *z*-score greater than the UK population ($P<0.01$), and in women those with the largest WC had a 15-fold increased risk of two cardiometabolic risk factors ($P<0.001$), and 3–6 fold greater impairment of specific QoL SF-36 domains ($P<0.05$).
Conclusions
Height prognosis has improved over time but delayed diagnosis is associated with shorter stature. Short stature was associated with hypertension but obesity had a greater impact on health than stature. We hypothesise that exposure to high androgens and/or excessive glucocorticoid treatment in childhood could reduce height and program hypertension.
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OC5.3

Mitotane induces endoplasmic reticulum stress triggering apoptosis and decrease of steroid hormone synthesis

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Background
Mitotane is the only drug approved for treatment of adrenocortical carcinoma (ACC). Molecular events leading to cell death in adrenocortical cells are unknown preventing the development of drugs with improved efficacy-toxicity ratio.
Methods
We employed the ACC model cell line NCI-H295 to investigate the effects of mitotane on genome-wide mRNA expression using microarray analysis. Several algorithms were used to delineate signaling pathways triggered by mitotane. Changes of steroid hormone production, apoptosis rate and cholesterol metabolism were measured.
Results
In dose-finding experiments, we confirmed the results of others showing inhibition of cortisol secretion and increased apoptotic rate by mitotane (EC50: 9.4 μM(3.12 mg/l) and 11.9 μM(3.9 mg/l) respectively). Microarray analyses showed profound changes in the expression profile of NCI-H295 cells after 6 h exposure to mitotane (459 and 1867 genes at 50 μM and 100 μM mitotane respectively). Among the top 30 downregulated genes several are implicated in sterol metabolism and steroidogenesis such as LDL-receptor, stearyl coA-desaturase, sterol-responsive element binding factor 1, and the cholesterol exporter ABCG1 (ATP-binding cassette subfamily G member 1). Most upregulated genes play a role in apoptosis such as GDF15, DUSP4, TRIB3, and CHOP. Unsupervised pathway analyses revealed endoplasmic reticulum (ER-) stress response among the pathways most significantly altered by mitotane. Accordingly, we found an increase of XBP1 mRNA-splicing pointing to activation of the most conserved pathway of ER-stress induction. ER-stress inhibitor salubrinal partly reversed mitotane-induced expression of ER-stress marker CHOP while ER-stress inducer thapsigargin increased the mitotane effect. Finally, strong and rapid intracellular accumulation of fluorescently labeled cholesterol was detected in mitotane-treated NCI-H295 cells but not in other cells.
Conclusion
Our data provide strong evidence for a key role of mitotane-induced endoplasmic reticulum stress in its adrenal specific toxicity. We hypothesize that intracellular overload of sterols triggers the canonical ER-stress pathway which eventually leads to increased apoptosis and diminished steroidogenesis.
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OC5.4

MUC-1 – a novel preclinical model for adrenocortical carcinoma

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Only two human cell lines are available for adrenocortical carcinoma (ACC) which do not reflect the functional heterogeneity of individual patient tumors and metastases. To overcome the lack of preclinical models for testing of novel therapeutic options in recent years we aimed at the development of patient-individual tumor models for endocrine tumors. Therefore, pieces of surgically excised patient tumors were implanted subcutaneously in the neck of athymic nude mice. To investigate whether morphological and functional characteristics between tumor samples after mouse engraftment in comparison to the original tumor would be comparable, we examined vitality, proliferation, vascularization and endocrine markers of the explanted material and the original patient tumor. During these studies one xenograft (MUC-1), derived from a neck metastasis of an ACC, showed extraordinary engraftment properties and sustained tumor growth over several passages in the murine host. Immunohistochemical analysis of explanted tumors revealed highly vascularized tissues of SF-1 positive cells with Ki67 indices of $37.7\pm0.8\%$. Transplanted mice had measurable cortisol levels of 2.7 μg/dl suggesting persistent glucocorticoid production by tumor cells. During ongoing studies we were able to utilize MUC-1 tumor bearing mice as an *in vivo* model in addition to the classical NCIh295-xenografts to investigate putative practicability in preclinical therapeutic settings. In an attempt to furthermore allow *in vitro*applications we established a primary culture based on explanted xenograft pieces which shows upon several passages promising proliferative characteristics with a Ki67 index of $38.6\pm3.2\%$ and sustained SF-1-expression. In ongoing experiments we are currently aiming at the overall characterization of MUC-1 to potentially provide a third preclinical tumor model for ACCs.
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OC5.5

Validation of follicular thyroid cancer molecular classifier in fine-needle aspiration biopsy samples

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Introduction
Follicular adenomas (FTA) and carcinomas (FTC) are thyroid tumours that are indistinguishable in the fine needle aspiration biopsy (FNAB). In our previous research we concentrated on post-operative material and developed the classifier, which discriminates the FTC and FTA, based on formalin-fixed paraffin-embedded (FFPE) material. The classifier was based on expression of five genes and gave the promising sensitivity of 71% and specificity of 72%. The aim of the current study was to validate that classifier on pre-operative fine-needle aspiration biopsy (FNAB) samples.
Material and methods
Tumour fine needle aspiration biopsy samples were derived from 9 FTC patients and 8 FTA patients. RNA was isolated using QIAGEN RNeasy Micro Kit. PCR amplification was performed with Universal Probe Library fluorescent probes (Roche) and 5′-nuclease assay, starting from 50 ng of total RNA. Normalization was carried out in the GeNorm application. The Diagonal Linear discriminant analysis (DLDA) method was used as a classification algorithm. The leave-one-out cross-validation (LOOCV) was used to assess the classifier performance.
Results
We measured the expression of five genes (ELMO1, EMCN, ITIH5, KCNAB1, SLCO2A1) in FNAB thyroid samples. We normalised the data and performed the classification in LOOCV loop. We calculated the performance of the FTC classification and obtained the accuracy of 71%, sensitivity of 67%, specificity of 75%, PPV of 75% and NPV of 67%.
Conclusions
We validated a simple FTC classifier that is based on the expression of five genes (ELMO1, EMCN, ITIH5, KCNAB1, SLCO2A1). We confirmed that it is useful in the discrimination of FTC and FTA when applied to FNAB samples.

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Bone, calcium & vitamin D

OC6.1

Ucma as a direct common target of Runx2 and Osterix promotes osteoblast differentiation

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Runx2 and Osterix(Osx) have been known as the master transcription factors for bone formation. However, genes that act downstream of both Runx2 and Osx have not been fully studied. To investigate downstream target genes of Runx2 and Osx, DNA microarray was conducted in calvaria of WT, $Runx2^{\Delta C/+}$, $Osx^{+/-}$, and $Runx2^{\Delta C/+}$; $Osx^{+/-}$ double heterozygous mice designated WT, $Runx2^{het}$, Osx^{het}, and $Double^{het}$ respectively. Compared to WT, the expression of Ucma, an unique cartilage matrix-associated protein, was decreased in $Runx2^{het}$ or Osx^{het} and it was more decreased in $Double^{het}$. In contrary, Ucma expression was increased in either Runx2 or Osx overexpressed osteoblasts and it was more increased in both Runx2 and Osx overexpressed osteoblasts. To examine Ucma expression during osteoblast differentiation, MC3T3-E1 osteoblastic cells were cultured for 30 days in the medium supplemented with ascorbic acid and β-glycerophosphate. Ucma expression exhibited in the middle of differentiation and continued during differentiation. To investigate whether Runx2 and Osx modulate the transcriptional activity of Ucma, Ucma promoter was co-transfected with Runx2 and/or Osx expression plasmid into MC3T3-E1 cells. The transcriptional activity of Ucma promoter was more increased when both Runx2 and Osx expression vectors were used. In Ucma promoter, two Sp1 and three Runx binding sites were existed. The Runx2- and Osx-mediated activations of Ucma promoter were directly regulated through Runx and/or Sp1 binding sites. The formation of mineralized nodules in Ucma-overexpressing stable clone was earlier and more increased than those of the mock control. Moreover, mineralized nodule formation was highly increased in MC3T3-E1 cells cultured in the medium including Ucma proteins secreted from Ucma-overexpressing cells. Collectively, this study suggests that Ucma is a novel downstream target gene regulated by both Runx2 and Osx and has a positive effect to enhance osteoblast differentiation and nodule formation.

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OC6.2

High spontaneous osteoclastogenesis in pediatric osteogenesis imperfecta patients receiving or not intravenous neridronate

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Background
Osteogenesis imperfecta (OI) is a heritable disease of the connective tissues caused primarily by heterogeneous mutations in the genes encoding for type I collagen. Phenotypically, it is characterized by abnormal bone mineralization, tissue fragility, and skeletal deformities.
Objective
The aim of this study was to investigate the osteoclastogenic potential of unfractionated peripheral blood mononuclear cells (PBMCs) from OI patients (mean age 10.44 ± 3.48) who received cyclical neridronate infusions for at least 1 year, untreated OI patients and control subjects.
Methods
PBMCs from six patients and six controls were cultured in presence/absence of M-CSF and RANKL. At the end of the culture period, mature multinucleated OCs were identified as TRAP+ cells. By real-time PCR we studied gene expression in freshly isolated PBMC. By flow cytometry we characterized the presence of OC precursors (CD14+/CD16+) and we studied TNF-alpha expression.
Results
Spontaneous formation of osteoclasts, without adding M-CSF and RANKL, occurred in PBMC cultures from treated and untreated OI patients. In these patients, the percentage of circulating osteoclast precursors, CD14+/CD16+ cells, increased respect to the controls (12.5% vs 0.1%, $P < 0.01$). By RT-PCR, we found high levels of RANKL, TNF-alpha and MCSF receptor, as well as decreased OPG levels, thus leading to the increase of RANKL/OPG ratio. High TNF-α levels were also found on monocytes through flow cytometry.
Conclusion
We showed for the first time the high osteoclastogenic potential of PBMCs from young OI patients, treated and untreated with bisphosphonate, which could be due to the high percentage of circulating OC precursors, to the elevated TNF-alpha levels as well as to the increased RANKL/OPG ratio. This condition could contribute to the bone disease affecting these patients.

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OC6.3

Hypoparathyroidism: The burden of illness and impact on patients' personal lives

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Hypoparathyroidism, a rare endocrine disorder of insufficient parathyroid hormone, leads to hypocalcemia and often hyperphosphatemia. The PARADOX study assessed the clinical and personal disease impact from the affected patients' perspective.

Patients ≥18 years and diagnosed ≥6 months ago completed a non-validated, self-reported, web-based survey.

Three hundred and seventy-four US adults (mean age, 49 years; women, 85%; mean disease duration, 13 years; self-reported severe disease, 31%) completed the study. Patients reported visiting a mean of 6 physicians before and after diagnosis; 48% strongly agreed to feeling mismanaged at diagnosis, and 79% strongly agreed that most physicians do not understand hypoparathyroidism. Patients visited their current physician a mean of 4 times/year. The majority strongly agreed that they felt unprepared to manage hypoparathyroidism at diagnosis (56%), that controlling their hypoparathyroidism was harder than expected (60%), and that they were concerned about long-term complications of their medications (75%). Despite current management regimens, 72% experienced >10 symptoms in the preceding 12 months and for a mean of 13 h/day. Symptoms reported by >75% of patients were fatigue (82%), muscle pain/cramping (78%), and paresthesia (76%). 259 patients (69%) experienced comorbidities, most frequently cardiac arrhythmias (66%) and kidney stones (36%). Hospital or ER visits were reported by 79% of patients; the annualized rate exceeded the US average (ER visits, 0.8 vs 0.4; hospital stays, 1.3 vs 0.6). Significant interference with daily life was reported by 45% of patients, an inability to perform some household activities by 85%, and a disease-associated change in employment status by 20%, of whom 44% reported a disabled employment status.

To our knowledge, this is the largest, most comprehensive study conducted to assess the impact of hypoparathyroidism from the patients' perspective. Despite the current standard of treatment, patients have a high burden of illness and experience various daily symptoms, with multifaceted effects on their lives.

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OC6.4

The REPEAT Study: An open-label clinical trial evaluating the safety and efficacy of recombinant human parathyroid hormone, rhPTH(1–84), for the treatment of hypoparathyroidism in hungary

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In hypoparathyroidism, inadequate levels of parathyroid hormone (PTH) result in hypocalcemia and often hyperphosphatemia. Large doses of calcium (Ca) and active vitamin D are typically used to manage symptoms, although these are often associated with complications and do not address the underlying PTH deficiency. In the phase III REPLACE trial, 24 weeks of treatment with rhPTH(1–84) was associated with maintained serum Ca without urine Ca excretion increases despite clinically meaningful reductions in oral Ca and active vitamin D in adults with hypoparathyroidism.

This open-label, 24-week study of subcutaneous rhPTH(1–84) was an extension of REPLACE. Patients received 50 μg/day rhPTH(1–84) (escalated to 75 and then to 100 μg/day, if needed, to reduce active vitamin D and oral Ca). The primary endpoint was defined as a ≥50% reduction from baseline in oral Ca and active vitamin D (or oral Ca ≤500 mg/day and calcitriol ≤0.25 μg/day or alfacalcidol ≤0.50 μg/day) and maintenance of serum Ca within normal limits.

Twenty-four patients [$n=16$ previously treated with rhPTH(1–84); $n=8$ rhPTH(1–84)-naive] enrolled (mean age, 52.7±10.9 years; 88% women; mean disease duration, 15.1±12.6 years). On average, 10.4 weeks elapsed between completion of REPLACE and REPEAT enrollment. At Week 24, 18/24 (75%) patients met the primary efficacy endpoint; 14/24 (58%) patients eliminated all oral Ca and active vitamin D. Treatment-emergent adverse events (TEAEs) were reported by 22/24 (92%) patients. The most common TEAEs were hypoesthesia (12/24 (50%)); muscle spasms and decreased vitamin D (both 6/24 (25%); unrelated); hypercalcemia (5/24 (21%)); fatigue, headache, and hypocalcemia (all 4/24 (17%); unrelated). No serious AEs occurred; no patients discontinued because of AEs.

rhPTH(1–84) 50, 75, or 100 μg/day was generally well tolerated. For the 16 patients who previously received rhPTH(1–84) in REPLACE, efficacy was sustained over long-term treatment.

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OC6.5

The effect of recombinant human parathyroid hormone, rhPTH(1–84), on vitamin D metabolism and phosphate homeostasis: Results from phase III 24-Week REPLACE and phase I clinical studies

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PTH promotes conversion of 25-hydroxyvitamin D (25[OH]D) to 1,25-dihydroxyvitamin D ($1,25[OH]_2D$), thus stimulating intestinal calcium and phosphate absorption. Because of low PTH levels in hypoparathyroidism, patients are prescribed calcitriol. Patients are predisposed to hyperphosphatemia owing to loss of PTH-stimulated phosphate excretion by the kidneys. Effects of rhPTH(1–84) on vitamin D metabolism and serum phosphate were studied.

In the phase I C09-002 study, patients received single 50-μg ($n=6$) and 100 μg ($n=7$) injections, separated by a ≥7-day washout. In REPLACE, patients were randomized to placebo ($n=44$) or rhPTH(1–84) ($n=90$) 50 μg/day (escalated to 75 and then 100 μg/day, if needed) while calcium or active vitamin D doses were reduced.[1]

In C09-002, mean±SD serum $1,25(OH)_2D$ levels increased following rhPTH(1–84) by 27.2±18.3 pg/ml (50 μg) and 19.6±11.0 pg/ml (100 μg) at 8–16 h. In REPLACE, 53% of rhPTH(1–84)-treated patients achieved ≥50% reduction in calcium and active vitamin D while maintaining serum calcium (placebo, 2%; $P<0.001$).[1] 43% of rhPTH(1–84)-treated patients achieved active vitamin D independence and took ≤500 mg/day calcium by Week 24 (placebo, 5%; $P<0.001$). Although active vitamin D doses decreased by 78% (rhPTH(1–84)) and 30% (placebo; $P<0.001$), serum $1,25(OH)_2D$ levels were maintained 24 h post-injection while 25(OH)D levels decreased by 11.2 ng/ml (rhPTH(1–84)) and 1.4 ng/ml (placebo).

In C09-002, rhPTH(1–84) decreased serum phosphate levels by 1.5 mg/dl at 5 h, increased 24-h urinary phosphate by 51% (50 μg) and 60% (100 μg), and decreased calcium-phosphate product by 11%–15% at 12 h. In REPLACE, lower serum phosphate levels following rhPTH(1–84) were maintained at Week 24 vs no change with placebo ($P\leq0.003$). Decreases in calcium-phosphate product were greater with rhPTH(1–84) than placebo ($P<0.001$).

rhPTH(1–84) normalized serum calcium and maintained serum $1,25(OH)_2D$, despite reduced active vitamin D intake, and restored phosphate homeostasis in these hypoparathyroidism studies.

Reference

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IGF-1 and Thyroid Basic

OC7.1

GH induces chemoresistance in human endometrial cancer cell lines involving ERK 1/2 and PKCdelta

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Background

Surgery is the main therapeutic option for advanced endometrial cancer; however, when disease relapses, chemotherapy is the only option. Chemoresistance is a very common phenomenon in these tumors. We previously demonstrated that GH protects breast cancer cells towards the cytotoxic effects of doxorubicin, inducing chemoresistance. Recent evidences show that endometrial cancer cells secrete GH, stimulating their own growth in an autocrine fashion.

Aim

To evaluate whether GH may impact on sensitivity of HEC1A and AN3CA endometrial cancer cell lines to Doxorubicin (D) and Cisplatin (C) and to investigate the possible implicated mechanisms.

Methods

Two endometrial cancer cell lines were used to carry out this study: the HEC-1A cell line, expressing the estrogen receptor (ER), and the AN3CA cell line, which does not express ER. To evaluate cell viability we performed ATPlite assay and to assess apoptosis activation we performed a Caspase 3–7 activity assay. To

evaluate protein expression, we performed western blot analysis.
Results
GH protected endometrial cancer cells from D- and C-induced apoptosis. In addition, GH reduced D- and C-induced ERK 1/2 phosphorylation and PKCδ expression, both involved in chemotherapic-dependent apoptosis. These effects were reduced by Pegvisomant, a GH receptor antagonist.
Conclusion
GH promotes resistance to apoptosis induced by chemotherapeutic drugs by modulating the apoptotic pathway, inhibiting ERK1/2 phosphorylation and PKCδ expression. These findings support the hypothesis that blocking GH receptor may be viewed as a potential new therapeutic approach to overcome chemoresistance in endometrial cancer.

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OC7.2

The proposed molecular mechanism underlying isolated growth hormone deficiency (IGHD) caused by C53S mutation

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Background
Besson A et al. described a patient with homozygous for C53S-hGH suffering from IGHD (JCEM2005 90:2493-9). They observed reduced ability of the mutant to bind and activate GHR in vitro. C53A-hGH lacks the disulfide bond between C53 and C165, which is conserved in GH/prolactin family.
Methods
Mouse pituitary AtT-20 cells, HEK-293 and CHO-K1 cells were transfected with plasmids containing C53S, C53A or C53S/C165A cDNA. hGH from cell supernatants and lysates was characterized with special immunoassays, western blots, a GHBP binding assay and proliferation assays using BaF-B03 and Nb2 cells.
Results
Western blot analysis of the AtT20 cell lysates under non-reduced conditions demonstrated the main band of C53S-hGH at 44 kDa, which could be reduced to lower molecular mass (22 kDa, 24 kDa) bands. However, C53S-hGH in supernatants of transfected AtT-20 cells appeared as both lower molecular mass and 44 kDa bands. In contrast the supernatants and lysates from HEK-293 and CHO-K1 cells contained mainly lower molecular mass C53S-hGH. In addition, the levels of C53S-hGH in supernatants and lysates from AtT-20 cells were only 32.0% and 9.8% of wt hGH levels respectively ($P<0.001$). C53S-hGH dimer exhibited very low binding to GHBP. The secreted C53S-hGH showed also reduced binding to GHBP (IC50 12.0 vs 3.0 nM, $P<0.001$) and decreased bioactivity in BaF-B03 assay (EC50 0.167 vs 0.036 nM, $P<0.05$) and in NB2 assay (EC50 0.150 vs 0.037 nM, $P<0.01$) compared to wt-hGH. The C53A-hGH mutation yielded the same results. In contrast, the double mutant C53S/C165A was unable to form a hGH dimer.
Conclusions
The unpaired cysteine at C165 in the C53S-hGH mutant leads to formation of a non-native disulfide bond linking two hGH molecules in pituitary cells. The C53S-hGH dimer possesses very low bioactivity. The production and secretion of C53S-hGH from pituitary cells was significantly reduced.

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OC7.3

Targeting the insulin-like growth factor 1 (IGF1R) and insulin (IR) receptor with a dual IGF1R/IR inhibitor, OSI-906, to potentiate mTOR inhibitor effects in experimental models of hepatocellular carcinoma (HCC)

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The mTOR and IGF/insulin pathways are frequently dysregulated in HCC. Antitumoral activity of mTOR inhibitors (mTORi) has been demonstrated in experimental models but in early clinical studies mTORi alone have shown modest antitumoral activity. IGF/insulin-dependent Akt activation, via IGF1R and IR, has been suggested as potential mechanism for mTORi resistance. This study aimed at evaluating the expression of mTOR and IGF/insulin pathway components and the effects of mTORi alone and in combination with the dual IGF1R/IR inhibitor, OSI-906, in human HCC cell lines HepG2 and HuH7. Expression of mTOR and IGF/insulin pathways components was evaluated by qRT-PCR. The effect of rapamycin (RAP), OSI-906 and combined treatment (CT, RAP 10^{-10}M plus OSI-906 10^{-6}M) was evaluated after 3 days on: cell proliferation (DNA assay), cell secretion (AFP concentrations, CLIA assay), cell cycle (FACS), cell migration (Scratch assay), cell invasion (Matrigel assay), and signaling pathways (WB). Both cell lines express mTOR components, IGF1R and IR and high levels of IGF2. Both RAP ($P<0.0001$) and OSI-906 ($P<0.01$) inhibited cell proliferation; CT had additive effects ($P<0.001$). Similarly, both drugs significantly suppressed AFP secretion with no additive effect of CT. OSI-906 ($P<0.01$) but not by RAP blocked cell cycle in G0/G1, with CT showing additive effects ($P<0.001$). In HuH7, OSI-906 ($P<0.001$) but not RAP inhibited cell migration with CT showing additive effects ($P<0.0001$). RAP ($P<0.0001$), OSI-906 ($P<0.0001$) and CT ($P<0.0001$) blocked cell invasion. HepG2 did not show invasion capability and both RAP and OSI-906 did not have effect on migration. Preliminary data on cell signalling demonstrated inhibition of ERK1/2, Akt and p70S6k activation after CT in HepG2. In conclusion, the results of the current study provide evidence that the combination of RAP and OSI-906 has an additive inhibitory effect on cell proliferation and cell cycle block by preventing Akt activation in experimental models of HCC.

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OC7.4

Training MCT10 to transport thyroxine: Structure based targeted mutations in MCT10

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With the identification of mutations in the monocarboxylate transporter 8 (MCT8) gene in patients afflicted with the Allan–Herndon–Dudley syndrome (AHDS), the concept of transporter-mediated transmembrane transport of thyroid hormones was finally accepted. Impaired thyroid hormone transport into neurons and pituitary cells is believed to cause severe psychomotor retardation and altered thyroid hormone function tests. MCT8 is a specific thyroid hormone transporter able to transport T4, T3, rT3, and 3,3′-T2, but does not transport D-enantiomers or related compounds lacking amino or carboxyl functional groups. MCT10 is a highly related thyroid hormone transport protein which is also known as TAT1 or T-type amino acid transporter. MCT10 transports T3 and aromatic amino acids, but not T4.
Based on a homology model of MCT8, we have identified 8 amino acid differences between MCT8 and MCT10 that are located along the presumed substrate translocation channel. We hypothesized that creation of chimeric transporters by exchanging these amino acids should alter MCT10 substrate preferences in $MCT10^{MCT8}$ chimeric proteins. If successful, we expect that $MCT10^{MCT8}$ would expand its substrate spectrum to include T4. An interesting question would then be whether the mutant $MCT10^{MCT8}$ would still be able to transport Trp or Tyr or whether T4 and aromatic amino acid transport are mutually exclusive.
We created several single and compound mutants of MCT10 with amino acid exchanges as found in MCT8 and tested their ability to transport T4 and Tyr in transfected MDCK-1 cells and *Xenopus* oocytes respectively. We will present data on a $MCT10^{MCT8}$ that is able to transport T4 and show its activity towards Tyr.
In summary, our data demonstrates that structure-guided site-directed mutagenesis can serve to identify amino acids important for substrate recognition. In turn, these findings support the usefulness of our model.

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OC7.5

Direct triiodothyronine effects in brown adipocytes

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Introduction
Thyroid hormones (TH) are essential regulators of metabolism and increase energy expenditure (EE). Mitochondria-rich brown adipose tissue (BAT) is specialised in thermogenesis and significantly contributes to EE. BAT contains essential components of TH action but TH transporters like MCT8 have not been characterised so far. As direct effects on O2 consumption and mitochondrial action have not been investigated before we tested MCT8 expression and direct effects of T3 in a BAT cell line.
Methods
We treated our previously described immortalised murine BAT cell line with triiodothyronine (T3) for 24h, determined MCT8 expression, and assessed aspects of mitochondrial function using immunohistochemistry, western blotting, ADP/ATP measurements, electron microscopy (EM) and oxygen consumption.
Results
Brown adipocytes express MCT8 transporters immunohistochemically. Administration of T3 did not cause any ultrastructural changes of mitochondria, as analysed by EM. Using western blotting with specific antibodies targeting TOMM20 and ATP synthase subunit beta, mitochondrial mass did not change. Mitochondrial autophagy as monitored by BNIP3 protein levels decreased slightly whereas PGC1alpha, a master regulator of mitochondrial biology, increased significantly. Oxygen consumption increased significantly and time-dependently upon T3 treatment and inner mitochondrial membrane potential decreased in parallel. No relevant alterations of ADP and ATP concentrations were detected.
Conclusions
This is a first functional demonstration of a direct T3 action on mitochondrial physiology in BAT cell lines, which express all components for T3 action including the TH transporter MCT8. Our data correspond well with metabolic adaptions seen after systemic TH treatment of rodents and humans and indicate an important effect of T3 independent of the central nervous system.

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Pituitary clinical

OC8.1

Metabolic improvement after treatment of acromeglay is determined by the increase of gynoid fat mass and the decrease of serum vaspin and IGF1

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Context
Adipose tissue distribution is closely related to metabolic disease risk. GH reduces visceral and total body adipose tissue mass, while inducing whole body insulin resistance.
Objective
To assess the role of visceral adipose tissue and derived adipokines for the systemic insulin resistance and lipid metabolism, before and after treatment in acromegaly.
Patients
Sixty-six adult patients with active acromegaly diagnosed between 2005–2013 at a tertiary referral center were evaluated before ($n=66$, 24 female, 42 male, age 48.8 ± 13.9), and after ($n=28$) different treatments (somatostatin analogues or/and transphenoidal surgery).
Outcome Measures
HOMA-IR was derived from fasting glucose and insulin. Body composition and visceral adipose tissue (Dual-energy X-ray Absorptiometry, Lunar Prodigy), lipid profile (total-, HDL-, LDL- cholesterol, Lp(a), ApoA, and ApoB), hsCRP, and selected adipokines (adiponectin, leptin, vaspin and omentin) were measured. The determinants for the baseline HOMA-IR and the change after treatment were explored in a stepwise multivariate linear regression model.
Results
At baseline, HOMA-IR was best predicted by total trunk fat mass and IGF1 ($r^2=0.44$, $P=0.002$). GH was negatively correlated with all the adipose tissue depots (arms $r=0.60$, legs $r=0.42$, trunk $r=0.75$, visceral $r=0.49$, and total $r=0.66$, $P<0.001$ for all) and positively with serum vaspin ($r=0.25$, $P=0.046$). After treatment, all the adipose tissue depots increased significantly, whereas HOMA-IR decreased. Vaspin decreased (0.32 (0.53) vs 0.18 (0.30) ng/ml, $P<0.001$), omentin increased (430 ± 129 vs 499 ± 149 ng/ml, $P=0.001$), while no significant change was observed for adiponectin and leptin. Although lipid profile improved, hsCRP increased (0.25 (0.3) vs 0.7 (1.9) mg/l, $P<0.001$).
Conclusions
Glucose and lipid metabolism parameters improved after treatment despite an increase of visceral and total adipose tissue. In contrast to other metabolic disorders, visceral adipose tissue mass was a weaker determinant of the baseline and the change of HOMA-IR compared to the total trunk fat mass. Vaspin may have a possible pathogenic role in insulin resistance of acromegaly.

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OC8.2

Soluble α-Klotho – a new serum biomarker for the activity of acromegaly

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Introducing
Acromegaly is characterized by excessive GH and IGF1 secretion. Recent date suggests that soluble α-Klotho is also elevated in patients with acromegaly.
Objective
The aim of this study was to assess the serum levels of soluble α-Klotho in patients in relation with the activity of disease and to compare with control group (CG). We also examine the relationship between excess GH, IGF1 and serum levels of soluble α-Klotho in patients with acromegaly and in the control group.
Methods
We studied 75 patients dived into two groups: I (56 patients with acromegaly) and II (29 healthy subjects as the CG. First group was divided into three subgroups accordingly to minimal GH concentration during the oral glucose tolerance test (OGTT) and IGF1 concentration: surgically cured acromegalic (SCA), well-controled acromegalic (WCA) and active acromegaly (AA) groups.
Results
Soluble α-Klotho was the highest in AA group and the smallest in SCA group. The differences of soluble α-Klotho levels were statistically significant when AA group were compared to SCA, WCA and CG groups ($P<0.000$, $P<0.002$, $P<0.001$ respectively). The difference was statistically significant when AA group was compared to SCA+WCA group ($P<0.000$). Soluble α-Klotho positively correlated with GH levels in WCA and WCA + SCA groups ($r=0.666$, $P<0.009$; $r=0.366$, $P<0.047$ respectively) and with IGF1 level in AA group ($r=0.589$, $P<0.021$).
Conclusions
The level of soluble α-Klotho is increased in active acromegalic patients. The markedly increased level of soluble α-Klotho in active acromegaly patients normalize after successful treatment in SCA and WCA groups. Soluble α-Klotho could be a new specific biomarker reflecting activity of disease in acromegaly.

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OC8.3

Assessment of atrial electromechanical delay in patients with acromegaly

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Aim
Cardiac rhythm abnormalities have been documented in acromegalic patients. Our aim is to evaluate atrial electromechanical delay (EMD) with tissue doppler imaging (TDI) in patients with acromegaly.

Material and methods
Fourty patients with acromegaly (13 patients with remission disease and 27 patients with active disease; 22 women and 18 men; mean aged 46.1 ± 10.3 years), and 37 age- and sex-matched healthy controls were enrolled in the study. Atrial conduction times of right atrium, left atrium and interatrial septum were measured by 2- dimensional TDI using a 3.5- MHz transducer (GE-Vingmed Ultrasound AS, Horten, Norway). Statistical analysis was performed on the basis of three groups; controls, active acromegaly (AA) and remission acromegaly (RA).
Results
Left atrial conduction time was found as 61.54 ± 13.13 ms in RA patients, 63.44 ± 13.69 ms in AA patients, and 43.94 ± 10.29 ms in controls ($P=0.0001$). Right atrial conduction time was not found as statistically significant ($P>0.05$) (RA patients; 11.92 ± 3.84 ms, AA patients; 12.61 ± 4.49 ms and controls 12.12 ± 3.96 ms). Interatrial conduction time was found as 31.53 ± 8.0 ms for RA, 35.65 ± 8.96 ms for AA patients, and 22.79 ± 6.89 ms for controls ($P=0.0001$). There was not statistically significant difference in left atrial, right atrial and interatrial conduction times between RA and AA groups ($P>0.05$). However, there was significant delay in left atrial and interatrial septum conduction time between both patients group and controls (RA vs controls, $P=0.0001$ and AA vs controls, $P=0.0001$ for left atrial conduction time; RA vs controls, $P=0.003$ and AA vs controls, $P=0.0001$, for interatrial septum conduction time)
Conclusion
This study suggests that atrial conduction time is delayed in patients with acromegaly both in remission and active state. Atrial electromechanical delay can be a predisposition factor for increased arrhythmia in acromegalic patients. This must be evaluated with further studies.

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OC8.4

Normalization of urinary cortisol with the potent 11β-hydroxylase inhibitor LCI699 in patients with Cushing's disease: 22-week, multicentre, open-label study

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Background
A proof-of-concept study (LINC 1) demonstrated that after 10 weeks, LCI699 normalized UFC in 11/12 patients with Cushing's disease. This interim analysis of the first eight patients enrolled into a longer-term study (LINC 2) further evaluates LCI699 in Cushing's disease; the full analysis on all 19 enrolled patients is expected in time for the congress.
Methods
There were two study groups. Previous LINC 1 participants (follow-up cohort (FC)), who were off LCI699 for at least 8 months, were offered re-enrolment if baseline UFC > 1 × ULN. Twice-daily LCI699 was initiated at the penultimate efficacious/tolerable dose in LINC 1; doses were escalated as needed. Newly enrolled patients (expansion cohort (EC)) had baseline UFC > 1.5 × ULN. LCI699 was initiated at 2 mg bid (5 mg bid if baseline UFC > 3 × ULN). Dose was escalated every 2 weeks to 5, 10, 20 and 30 mg bid until UFC was ≤ ULN, whereupon that dose was maintained or reduced for safety reasons up to 22 weeks. Main efficacy endpoints were the proportion of responders (UFC ≤ ULN or ≧ 50% decrease from baseline) at weeks 10 and 22.
Results
Nineteen patients enrolled (FC, $n=4$; EC, $n=15$); eight are included in this interim analysis (FC, $n=2$; EC, $n=6$; male:female 3:5; aged 28–51 years); one EC patient discontinued after week 2 for AEs (diarrhoea/muscle weakness/malaise/papule). At week 10, 7/8 patients (87.5%) were responders (FC 2/2; EC 5/6). At week 22, 6/8 patients (75.0%) were responders (FC 1/2; EC 5/6); no responders required a dose increase during weeks 10–22. All responders at both time points had UFC ≤ ULN. The most common AEs were asthenia ($n=5$) and nasopharyngitis ($n=4$). Hypokalaemia developed in four patients. Three patients had ACTH > 2 × baseline at week 22. One patient experienced a hypocortisolism-related AE. There were no serious AEs.
Conclusions
This interim analysis demonstrates that 22 weeks' LCI699 treatment reduces UFC ≤ ULN in 75% of patients, with good tolerability.

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OC8.5

The effects of glucocorticoid treatment on cognition in patients with secondary adrenal insufficiency – results from a RCT

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Introduction
A wide variety in hydrocortisone substitution dose-regimens are considered physiological for patients with secondary adrenal insufficiency. However, it is likely that cognition is negatively influenced by higher cortisol exposure to the brain. So far, no studies have been performed to assess the effects of treatment regimens administered for a substantial period of time with a low physiological hydrocortisone dose in comparison to a high physiological hydrocortisone dose on cognition.
Methods
This randomized, double blind cross-over study included 47 patients (mean (S.D.) age, 51(14) years, range 19–73) with secondary adrenal insufficiency. Patients randomly received first a low dose hydrocortisone (0.2–0.3 mg/kg body weight) during 10 weeks followed by a high dose (0.4–0.6 mg/kg body weight) for another 10 weeks, or vice versa. Cognitive performance of patients was measured at baseline and after each treatment period. A battery of 11 standardized cognitive tests covering 4 cognitive domains (memory, attention, executive functioning and social cognition) was used.
Results
Patients in the high dose condition scored significantly worse on short term memory (15 Words Test, $P=0.028$, *Z-score* low dose (S.D.) = 0.35 (1.01), *Z-score* high dose (S.D.) = −0.03 (1.03), $d=0.38$) and showed a higher variability of reaction time in the phasic alertness task (Test of Attentional Performance, $P=0.015$, *Z-score* low dose (S.D.) = −0.14 (0.82), *Z-score* high dose (S.D.) = −0.42 (0.79), $d=0.35$) compared to patients in the low dose condition. A trend towards more impaired scores on social cognition ($P=0.065$) and fewer impaired scores on psychomotor speed ($P=0.092$) was observed in the low dose condition. No differences were found on the other measures of cognitive performance.
Conclusion
In patients with secondary adrenal insufficiency, a higher physiological dose of hydrocortisone has a negative influence on short-term memory and aspects of attention compared to a lower dose after 10 weeks of treatment.

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Reproduction

OC9.1

High frequency of *FGFR1* mutations in patients with congenital hypogonadotropic hypogonadism and split hand/foot malformation

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Background
Congenital hypogonadotropic hypogonadism (CHH) is characterized by absent puberty and infertility due to a lack of GnRH secretion/action. In addition,

patients exhibit variable non-reproductive phenotypes such as anosmia, cleft palate, synkinesia, and others. As many as 10% of CHH patients harbor mutations in *FGFR1;* this group is enriched for skeletal anomalies. We report here a novel CHH-associated skeletal phenotype, split hand/foot malformation (SHFM), defined as absent development of the central ray.
Methods
CHH patients exhibiting SHFM were identified from four international CHH cohorts. Probands and available family members underwent extensive phenotyping and were screened for mutations in *FGFR1*. The functional impact of identified mutations was assessed by homology modelling, crystallography-based structural predictions, and/or *in vitro* assays.
Results
We identified eight CHH probands exhibiting SHFM. Seven of these probands (88%) harbored *FGFR1* mutations, including one homozygous (p.V429E) and six heterozygous mutations (p.G348R, p.G485R, p.Q594X, p.E670A, p.V688L, p.L712P). They all exhibited severe GnRH deficiency with absent puberty; cryptorchidism and/or micropenis were present in 5/7. Incomplete penetrance and variable expressivity of phenotypes (olfactory/reproductive/SHFM) were observed among mutation carriers in each family. All mutations were predicted to be loss-of-function by homology and structural modelling. The V429E mutation maps to the FRS2 binding domain of FGFR1; functional studies demonstrated that it decreases recruitment and association of FRS2Θ to FGFR1, thereby resulting in reduced MAPK signalling.
Conclusion
SHFM is a novel CHH-associated phenotype. Mice with limb mesenchyme-specific knock-out of *Fgfr1* exhibit absent central ray development, thus phenocopying SHFM. *FGFR1* should be prioritized for sequencing in CHH patients with SHFM, because the likelihood of finding a mutation increases from 10% (general CHH population) to 88% (CHH + SHFM).

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OC9.2

Tadalafil ameliorates metabolic syndrome-induced alterations in visceral adipose tissue and liver: an experimental study in the rabbit

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Visceral adipose tissue (VAT) dysfunction is closely associated with the rising incidence of cardiovascular diseases (CVD) and type 2 diabetes mellitus. Two distinct types of adipose tissue, white (WAT) and brown (BAT), are present in mammals. Development of 'brown-like' adipocytes within white adipose tissue has potential antiobesity and insulin-sensitizing effects. Genetic manipulation of cGMP formation suggests a new role for this pathway in preadipocytes commitment. We have recently demonstrated that the selective phosphodiesterase type 5 (PDE5) inhibitor, tadalafil, by increasing cGMP signaling, reduced visceral adiposity (VAT) and triglycerides level in a high-fat diet (HFD)-induced rabbit model of metabolic syndrome (MetS). Herein, we investigated the effects of *in vivo* tadalafil dosing (2 mg/kg per day, for 1 week) on liver, VAT, and the adipogenic capacity on isolated VAT preadipocytes (rPADs) from rabbits fed a HFD (with or w/o tadalafil) or regular diet (RD). Results: Adipocyte size, tissue hypoxia, and the expression of cytosolic insulin-regulated glucose transporter GLUT4 were significantly increased in VAT isolated from the HFD rabbits, and normalized by *in vivo* tadalafil dosing. The circulating level and liver expression of TNFα was also increased in HFD rabbits and decreased by *in vivo* tadalafil dosing. rPADs isolated from the HFD rabbits were less sensitive to insulin, as demonstrated by the decreased insulin-induced glucose uptake, triglyceride synthesis, and adipogenic capacity, as well as by the impaired fusion of lipid droplets. *In vivo* tadalafil dosing preserved all the aforementioned metabolic alterations. Expression of UCP-1 was *in vivo* (VAT) and *in vitr* (rPAD) increased by tadalafil, which partially stimulates preadipocyte differentiation towards a brown-like phenotype.
In conclusion, Tadalafil dosing in a MetS rabbit model ameliorates liver and VAT MetS-induced alterations. This could reflect the ability of tadalafil to restore insulin sensitivity in VAT unable to finalize its storage function, counteracting MetS-induced liver alterations.

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OC9.3

Late onset hypogonadism influences the endothelial function in men with coronary artery disease

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Late onset hypogonadism (LOH) is common in men with coronary artery disease (CAD) but its interaction with endothelial function and arterial structural changes is debatable.
Aim
To investigate whether the LOH in men with CAD predicts endothelial dysfunction.
Methods
Two hundred consecutive men with CAD and successful coronary stent implantation or coronary artery bypass grafting were included to the study group (mean age 59 ± 10 years; acute coronary syndrome 78%, diabetes 29%, currently smokers 44%, hypertension 65%, BMI 29 ± 4.3 kg/m^2, left ventricular EF% 52 ± 10). All the patients received pharmacotherapy according to the actual ESC recommendations. Non-invasive methods for endothelial function evaluation – flow mediated dilatation of brachial artery (FMD%) and parameter of arterial structural changes – intima-media thickness of common carotid artery (IMT CCA) and common femoral artery (IMT CFA) were measured.
Result
The mean testosterone level in the whole group was 3.8 ± 1.5 ng/ml. LOH was diagnosed in 83 (42%) men. Patients with LOH had a higher hsCRP capacity than eugonadal: median 5 mg/l (25–75Q: 2.9 to 12.2 to 27) *vs* 3.2 mg/l (25-75Q: 1.3 to 8.8), $P = 0.007$; NT-proBNP level median 48 pg/ml (25–75Q: 241 to 686) *vs* 263 pg/ml (25–75Q: 102 to 616); $P = 0.008$. After adjusting for BMI, age, current smokers, NT-proBNP, left ventricular EF, hsCRP, in males with LOH FMD% was still significantly lower than in normal eugonadal males: 6.3 (95%CI: 5.2 to 7.4) *vs* 8.5 (95%CI: 7.6 to 9.4), mean difference 2.2 (95%CI: 0.8 to 3.6 $P = 0.002$). LOH didn't influence IMT CCA: mean difference 0.05 ($P = 0.17$) and IMT CFA mean difference 0.05 ($P = 0.77$).
Conclusion
LOH in males with CAD coexists with impaired endothelial but not with arterial structural changes. This relationship requires further investigation.

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OC9.4

Kisspeptin – a novel physiological trigger for oocyte maturation in IVF treatment

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Background
In vitro fertilisation (IVF) is an effective treatment for infertility, but can cause the ovarian hyper-stimulation syndrome (OHSS), which is associated with serous effusions, circulatory collapse, and even death. The use of human chorionic gonadotrophin (hCG) stimulates oocyte maturation during IVF, but is also the major cause of OHSS. The hypothalamic neuropeptide kisspeptin stimulates endogenous LH secretion in a GnRH-dependent manner. A more physiological stimulus for oocyte maturation may avoid OHSS and thereby improve the safety of IVF treatment.
Aim
To determine if kisspeptin can induce oocyte maturation during IVF treatment.
Methods
Fifty-three women underwent a modified recombinant FSH/GnRH antagonist IVF protocol, using kisspeptin instead of hCG to trigger oocyte maturation. Daily recombinant FSH treatment was commenced from menstrual day 2. A GnRH-antagonist was used to inhibit a premature LH surge. A single subcutaneous injection of kisspeptin (1.6–3.2 nmol/kg, $n = 5$; 6.4 nmol/kg, $n = 24$; 12.8 nmol/kg, $n = 24$) was administered to induce oocyte maturation. Oocytes were retrieved 36h after kisspeptin injection. Following intracytoplasmic sperm injection (ICSI), 1–2 embryos were transferred to the uterine cavity. Primary outcome was the number of mature oocytes (oocytes in metaphase II; MII).

Results
Kisspeptin increased serum LH 9.0±7.5 fold (mean±S.D.) 12 h following injection. Oocyte maturation was observed at all doses of kisspeptin: 96%(51/53), with 7.9±3.9 MII oocytes/cycle. Fertilisation occurred in 92%(49/53) cases, with 5.6±3.5 zygotes/cycle. Clinical pregnancy has been confirmed on ultrasound at 6 week gestation in 12/53(23%) patients receiving kisspeptin and to date 5 patients have already given birth to healthy babies.
Conclusion
We show for the first time that kisspeptin can effectively induce oocyte maturation in IVF treatment. Kisspeptin may therefore offer an entirely novel and potentially safer therapeutic option for fertility treatment.

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OC9.5

IGF1 gene polymorphism in Polycystic Ovary Syndrome

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Introduction
IGFs (Insulin like growth factors) are important regulators of pancreatic β-cell development, growth and maintanence. Mutations in the IGF genes have been found to be associated with type 2 diabetes, myocardial infarction, birth weight and obesity. These associations could result from changes in insulin secretion. Insulin resistance plays a key role in PCOS. Based on these findings, we aimed to investigate IGF1 gene polymorphism in polycystic ovary syndrome patients.
Methods
Eighty-six women with PCOS and 81 healthy women, recruited from the Endocrinology Clinic of Pamukkale University, were studied. The diagnosis of PCOS was based on the revised criteria of Rotterdam. Anthropometric measurements were performed. A fasting blood sample was obtained in the morning for measurement of glucose, insulin, PRL, LH, FSH, estradiol, total testosterone(T), sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulphate (DHEA-S), TSH and IGF1. Free androgen index and HOMA-IR values are calculated. Genomic DNA from the patients and controls were prepared.
Results
Women with PCOS had higher IGF-1, insülin, LH, SHBG and DHEAS levels, compared to controls. BMI and HOMA-IR values were higher in the PCOS group than in the control group. We studied the IGF-1 $(CA)_{19}$ polymorphism and categorized into three group as lower than192-bp(group 1), 192–194 bp (group 2), higher than 194-bp (group 3). There was no statistically significant difference for three subgroups between the patients and controls.
Conclusion
In this study we found no differrences in terms of IGF-1 CA19 polymorphism distribution between patients and control groups. In literature there are inconclusive results on whether IGF1 CA19 polymorphism is associated with IGF-1 levels, type-2 diabetes and myocardial infarction. Future prospective studies would be designed in large-scale PCOS populations which might identify underlying causal effect of IGF-1 CA19 polymorphism on PCOS phenotype.

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Endocrine Tumours

OC10.1

Blood-borne and tissue microRNAs in adrenocortical tumours: affected pathways and diagnostic relevance

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Background
The differential expression of tissue microRNAs in benign and malignant adrenocortical tumours has been described in several studies including ours. Novel data show that microRNAs are also present in the bloodstream and can be exploited as minimally invasive markers of malignancy.
Objective
To analyze the microRNAs expressed in different studies by an in silico approach and to establish the molecular pathways affected. Furthermore, circulating counterparts of selected tissue microRNAs were examined to evaluate their applicability as markers of malignancy.
Methods
MicroRNA and mRNA datasets have been subjected to tissue specific target prediction by an own software. Pathway analysis was performed by Ingenuity Pathway Analysis. Blood-borne counterparts of eight microRNAs reported as significantly differentially expressed in tissues have been studied by real-time qRT-PCR of total RNA isolated from plasma samples of patients with adrenocortical adenomas (ACA) and adrenocortical cancer (ACC).
Results
Eighty-five molecular pathways have been found in the ACA–ACC comparison that might be affected by the significantly differentially expressed tissue microRNAs commonly altered in at least two studies. These include novel pathways e.g. interleukin and growth factor signalling, integrin signalling, aryl hydrocarbon receptor signalling, etc. From the eight blood-borne microRNAs tested, five (*hsa-miR-483-5p, hsa-miR-181b, hsa-miR-100, hsa-miR-210, hsa-miR-184*) showed significant overexpression in ACC plasma samples relative to ACA using *hsa-miR-16* as reference gene. By ROC analysis, the combination of $dCT_{hsa\text{-}miR\text{-}210}$-$dCT_{hsa\text{-}miR\text{-}181b}$ and $dCT_{hsa\text{-}miR\text{-}100}$/$dCT_{hsa\text{-}miR\text{-}181b}$ showed the best sensitivity and specificity among blood-borne microRNAs as markers of malignancy and these are different from the best markers reported in adrenocortical tissues to date.
Conclusions
The numerous pathways affected may include pathways that might even represent potential novel therapeutic targets. Significant differences in expression of blood-borne plasma microRNAs have been established between ACA and ACC, but further studies will be needed to confirm their applicabililty in the clinical setting.

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OC10.2

The cytotoxic effect of sunitinib on human bronchial carcinoid cell lines and primary cultures is counteracted by EGF and IGF-1 but not by VEGF

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Background
Bronchial carcinoids (BC) are rare tumors originating from endocrine cells dispersed in the respiratory epithelium. The main BC treatment is surgery, which is not feasible for large, infiltrating and metastatic disease. In these settings, medical therapy is often tried. Therefore it is important to identify new therapeutic targets and new molecules capable of providing adequate medical treatment for patients with BC. Sunitinib, is an oral, small-molecule, multi-targeted receptor tyrosine kinase inhibitor (TKI).
Aim
To verify if sunitinib is active in inhibiting cell viability of human BC and what are its targets in these cells.
Methods
Human BC cell lines (NCH-727 and NCI-H727 cells) and human BC primary cultures were treated with sunitinib 5 μM and/or EGF 30 nM, IGF1 50 nM, or VEGF 10 nM. Cell viability and caspase 3/7 activation were measured after 48 h of treatment.
Results
Sunitinib is capable of inhibiting cell viability of BC cell lines and primary cultures (by 20–50% vs control); moreover sunitinib activates caspase 3/7 (by 20–100% vs control). Both events are counteracted by EGF and IGF-1 at concentrations similar to those found in plasma, but not by VEGF despite its receptors are usually considered the main target of sunitinib.
Conclusion
These data indicate that sunitinib is a potential therapeutic agent for treatment of BC, and that its mechanism of action could be mediated, at least in part, by EGFR and IGF1R. Further experiments are needed to deeply understand this issue.

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OC10.3

The NMU signaling controls cancer progression of human RL95-2 endometrial cancer cells through cell motility maintenance

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In addition to regular functions in controlling muscle contraction and energy homeostasis, recent studies have reported the neuromedin U (NMU) signaling plays important roles in cancer progression. Intriguingly, we observed that both NMU and one of its receptors, NMUR2, are highly expressed and co-localized in the mouse uterine endometrial luminal epithelium during the estrus stage. We also found that the *NMU* transcript is dramatically augmented in patients with high-grade endometrial cancers, suggesting that the NMU signaling may participate in the uterine cancer progression. Following these findings, RL95-2 and Ishikawa cells, the endometrial cancer lines with a high *NMU* transcript level, are used to investigate the roles of NMU signaling during endometrial cancer progression. Using *NMU* knockdown approaches, we demonstrated that the high level of NMU signaling is required for the maintenance of cell morphology and the ability of migration and invasion in RL95-2 cells, which is derived from the moderately-differentiation endometrial cancer, but not in the Ishikawa cells, which is derived from the well-differentiation endometrial cancer. Further, we found that *NMU* knockdown in RL95-2 cells not only decreases the basal transcripts but also attenuates the EGF- or TGFβ-induced levels of N-cadherin and vimentin, which are required for maintenance of cell morphology and cell motility. Low motility rate might dampen the spreading efficiency, restrict the growth space, and thus affect the growth rate of RL95-2 cells. Indeed, we did observe that RL95-2 cells with *NMU* knockdown grew in clusters and have a lower growth rate than the control cells under a prolonged culture condition. Taken together, these results suggest that the NMU signaling is critical for high-grade endometrial cancers and involved in the cancer progression through the regulation of cell motility.

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OC10.4

Mast cell interactions at tumour interface drive progression in human prostate cancer

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Introduction
Prostate cancer is hormone dependent and regulated by a balance of androgens as well as estrogens. Regulatory control is also exerted by the tumor microenvironment including cancer-associated fibroblasts (CAFs), and immune cells. Although patient derived xenografts (PDX) commonly used to study the functional effects of CAFs, the method is not quantitative, is lengthy, technically challenging and the xenografts are placed in immune suppressed hosts excluding immune cell contribution.
Methods
We developed a novel bioengineered cellularized co-culture to study stromal-immune cell interactions. Our novel system quantifies multiple cellular interactions between human tumour stromal fibroblasts and mast cells on epithelial tumour cell morphology, motility and invasion.
Results
First we show mast cell numbers are increased in human PCa clinical specimens, specifically within the peri-tumoural stroma. Using our bioengineered cultures we next show CAFs induce morphological changes in epithelial cells independent of the Gleason grade of the tumor of origin. However, when human mast cells were also added to the co-culture system, there was further and significant potentiation of the effects of CAFs on epithelial cells features. Further mechanistic studies showed estrogen (*via* ERalpha) mediates cooperation between CAFs and mast cells at the tumour interface. Human mast cells express ERα and ERβ, and estradiol directly stimulates mast cell proliferation and migration as well as altered cytokine/chemokine expression. Androgen signaling is reduced in CAFs, while ERα and ERβ transcriptional activity is not, allowing estrogen to dictate hormone action in the tumor microenvironment. Gene microarray analyses identified CXCL12 as a major estrogen driven target gene in CAFs, and CAFs recruit mast cells *via* CXCL12 in a CXCR4-dependent manner.
Conclusions
Collectively, these data reveal multicellular estrogen action in the tumormicroenvironment and show dominant estrogen signaling at the prostatic tumor interface.

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OC10.5

Molecular mechanisms underlying the unexpected promoting effects of mifepristone on murine testicular Leydig cell tumorigenesis

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Progesterone (P4) treatment has been shown to have a clear modulating effect on murine Leydig tumor cell (mLTC-1) function, including downregulation of luteinizing hormone receptor. We hypothesized that P4 would stimulate, whereas an antiprogestine mifepristone (MF) block tumor progression *in vivo* in a transgenic (TG) murine Leydig cell tumor model (inhibin-α promoter-driven SV40 T-antigen (inhα/Tag)) and act similarly on cell proliferation *in vitro*. Supra-physiological doses, up to 5 μM, of P4 and unexpectedly MF significantly stimulated cell proliferation in murine BLT-1 and mLTC-1 cell lines compared to non-stimulated controls. Similarly, 1 month treatment of P4 and MF *in vivo* (*vs* non treated controls), starting at 5.5 month of age, stimulated the progression of discernible Leydig cell tumor in inhα/Tag mice. The TG tumors, as well as BLT-1 and mLTC-1 cell lines, expressed nuclear progesterone receptors (PR) A and B, membrane PRs α, β, and γ and membrane components PGRMC1 and PGRMC2. Non-treated Inhα/Tag testes histopathologically presented with severe cellular atypia, only few peripheral tubular structures with spermatogenic cells up to elongated spermatids and a rapid tumor growth, some parts with necrosis and/or hemosiderin. In the P4- and MF-treated groups, testicular histopathology showed overall destroyed cellular morphology with blood filled cavities, infiltrating lymphocytes, and large parts with Leydig cell tumors with almost none of the normal testicular structures left. MF or P4 treatments upregulated *Tgfbr2* and *Alk1* and promoted alternative TGFβ pathway activation in inhα/Tag Leydig cell tumors. Moreover, MF treatment downregulated *Smad6* (inhibitor of ALK1 signaling) and upregulated *Smad7,* a blocker for SMAD2/SMAD3 complex; whereas P4 upregulated endoglin, co-receptor for TGFβ receptor complex. These findings provide novel mechanistic insights on selective PR modulator MF acting as P4 agonist and promoting Leydig cell tumorigenesis in inhα/Tag TG mice through pro-tumorigenic *Tgfbr2* signaling pathway.

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Diabetes and Obesity 2

OC11.1

Inhibition of cardiac dysfunction in diabetic mice by treatment with brain natriuretic peptide

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Aims/hypothesis
Obesity and diabetes enhance the risk of developing cardiovascular diseases and heart failure. These metabolic disorders are generally reflected by natriuretic peptides system deficiency. Since brain natriuretic peptide (BNP) is known to influence metabolism and cardioprotection, we investigated the effect of chronic exogenous BNP treatment on adverse myocardial consequences related to obesity and diabetes.

Methods
Ten-week-old C57BL/KsJ-*db/db* obese diabetic mice (*db*/*db*) and their lean control littermates (*db*/+) were treated with BNP (0.6 μg/kg per h) or saline during 12 weeks ($n=10$/group). Serial blood and tomography analysis were performed. Cardiac function was determined by echocardiography, and biochemical and histological heart and fat analysis were also performed.
Results
BNP treatment resulted in an average increase in plasma levels of 70 pg/ml. An improvement in the metabolic profile of *db*/*db* mice was observed, including a reduction in fat content, increased insulin sensitivity, improved glucose tolerance and lower blood glucose, despite increase food intake. *Db*/*db* mice receiving saline displayed both early systolic and diastolic dysfunction whereas these functional changes were prevented by BNP treatment. The cardioprotective effects of BNP were attributed to the inhibition of cardiomyocytes apoptosis, myocardial fibrosis, cardiac hypertrophy and advanced glycation end-products/receptor for advanced glycation end-products (AGE/RAGE) as well as normalization of cardiac 5′ adenosine monophosphate-activated protein kinase (AMPK) and endothelial nitric oxide synthase (eNOS) activities.
Conclusion/interpretation
This study demonstrated beneficial effect of chronic low dose infusion of BNP on metabolism profile together with the prevention of diabetic heart disease in *db*/*db* mice model. Cardioprotective mechanisms of BNP include normalization of cardiac AMPK and eNOS activities as well as a reduced cardiac AGE formation. These observations clearly suggest a potential role for BNP in replacement therapy for the prevention of cardiovascular complications of diabetes and obesity.

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OC11.2

An audit of the management of inpatient glycaemia using point of care testing data at Manchester Royal Infirmary

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Background
Suboptimal glycaemic control in hospital inpatients is related to poor clinical outcomes and longer hospital stay. The aims of this study were to document the prevalence and severity of hypo- and hyperglycaemia in medical inpatients and to evaluate aspects of patient management and staff proficiency regarding glucose management.
Methods
We performed a retrospective review of 21 381 capillary blood glucose results in 1496 unique patients on 26 inpatient wards during April 2013. We applied four audit standards (proportion achieving normo-glycaemia; appropriate diabetes team referral; re-checking of hypoglycaemia; proportion with correct patient identifier) to assess/rank ward performance.
Results
There was a large range in the proportion of inpatients with hypo- and hyperglycaemia between wards that was not readily explained by case mix (Hypoglycaemia: mild ($\leq$4.0 mmol/l), 1–18%; moderate ($<$3.0 mmol/l), 0–13%; severe ($<$2.2 mmol/l), 0–13%; Hyperglycaemia: mild ($>$10 mmol/l), 2–45%; moderate ($>$20 mmol/l), 0–19%; severe ($>$28 mmol/l), 0–8%). Overall, 9% of all inpatients had at least one blood glucose value $\leq$4 mmol/l and only 25% of patients were appropriately referred to the diabetes team following episodes of severe hypo/hyperglycaemia. Of the 774 hypoglycaemic blood glucose values, only 9% were re-tested within 15 min and only 85% of all tests were accompanied by a valid patient identifier.
Conclusion
The wide variation in ward performance and suboptimal glucose control overall has highlighted a need for intensive ward-based diabetes education focusing on some underperforming wards. We will improve visibility of glucose results for clinicians and make future ward performance data freely available within the trust to stimulate improvements in performance.

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OC11.3

Improvement or stabilization of retinopathy and visual acuity after islet transplantation: a 5-year prospective study

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This study describes the evolution of retinopathy 5 years after islet transplantation (IT) with the Edmonton protocol in type 1 diabetic patients. Before IT and then yearly for 5 years, 21 patients (13 islet-alone (ITA), 8 islet-after-kidney (IAK)) underwent monitoring of laboratory parameters, continuous 24 h mean blood pressure (24h BP) and 72 h glucose (CGM), as well as complete ophthalmologic examination. Ten of the 21 patients (48%) were insulin-independent 5 years post-IT (median (IQR) 5-year post-IT A1c: 6.9% (6.0–7.9); $n=21$; $P<0.001$). Four had lost their islet graft but were analyzed on an intention-to-treat basis. Before IT, 5/42 eyes were blind due to diabetes. A retinopathy was found in 26 of the remaining 37 eyes (70.3%) with panphotocoagulation in 19/37 eyes (51%). Five years post-IT, a stabilization of the retinopathy was found in 32/37 eyes (86%), and a mild worsening in 5/37 eyes (14%). No progression of a non-proliferative to a proliferative retinopathy was observed. Two vitreous bleeding occurred during the 1st year post-IT and spontaneously resolved in two different patients. Four patients required a photocoagulation during the 5-year follow-up period. There was no significant difference between ITA and IAK. The evolution of post-prandial blood glucose ($P=0.0004$), CGM-mean glucose ($P=0.0053$) and CGM–SD ($P=0.002$), but not of fasting blood glucose and C-peptide, ß score, GAD, lipids, blood pressure, diabetes duration, visual acuity, differed significantly between the groups worsening and stabilization. Five years post-IT, visual acuity (VA) had improved in 38% of the 37 eyes, stabilized in another 38% and worsened in 24%. Over the 5-year period, the mean VA did not change significantly in the whole group, but differed between ITA and IAK ($P<0.0001$), with a best and stable VA in ITA, and a greater benefit in IAK.
Conclusion
Islet transplantation enables to reach a 5-year insulin-independence rate close to 50% and a stabilization or improvement of retinopathy and visual acuity in 80% of cases.

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OC11.4

A novel adult human adipose stem cell model from inducible brown fat surrounding pheochromocytoma tumors

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The recent discovery of the presence of brown adipose tissue (BAT) also in human adults is pivotal for development of anti-obesity therapies. This type of fat, in fact, mainly consists of brite cells (brown adipocytes appearing for a browning process in white fat) which are involved in adiposity control. The origin of brite cells in adult white adipose tissue (WAT) is still unclear as human cell models are lacking.
Our study demonstrated the presence of BAT islets dispersed in periadrenal WAT of adult patients affected by pheochromocytoma tumors, secreting catecholamines. All the enrolled patients affected by pheochromocytoma ($n=8$, mean$\pm$S.D.: 48$\pm$19 years for age, 23.8$\pm$2.0 kg/m^2 for body mass index, BMI), but not the one with adenocortical adenoma, presented extensive

BAT islets in the fat surrounding the tumor lesion (uncoupling-protein-1 UCP-1 mean $2^{-\Delta\Delta Ct} \pm$ S.D. of the expression vs GAPDH:150134 ± 106137) and had elevated levels of urinary total metanephrines (normetanephrines + metanephrines mean ± S.D.: 4447 ± 1927 μg/24 h) which negatively correlated with BMI ($r = 0.854$, $r^2 = 0.730$, $P = 0.007$, $n = 8$). From this fat depot, expressing brite and classical markers in addition to high levels of UCP-1, for the first time, we isolated and characterized brown adipose stem cells (B-ASC) and compared their properties with precursors obtained from subcutaneous WAT (S-ASC) of the same patients. B-ASC showed mesenchymal, stem and multipotency features as well as expression of brite/classical markers. When differentiated toward white adipose phenotype, they accumulated more lipid droplets and smaller than the differentiated adipocytes deriving from S-ASC. Using specific brown differentiation cocktails, we could not obtain mature brown adipocytes but brown commitment only in B- and not in S-ASC.

In conclusion, we demonstrated the presence of BAT precursors, different from WAT, in fat surrounding pheochromocytoma lesions, representing a unique *in vitro* human stem cell model of brown adipose tissue to study brown adipogenesis and browning process.

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OC11.5

Lipodystophic laminopathies are characterised by an increased intra/whole abdominal fat ratio with preserved fat/lean mass ratio and hypoleptinemia, in contrast with obese people, compared to controls

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Introduction
The diagnosis of non-HIV lipodystrophies is challenging, especially since borderline forms with type 2 diabetes have been described (Strickland Diabetes Care 2013).
Objective
To identify the most specific anthropometric and biological parameters enabling to differentiate lipodystrophic from obese and control subjects.
Methods
This prospective study (clin.gov 2009-AO-1169-48) included 94 patients divided in 3 groups adjusted for age and gender: 52 lipodystrophic patients (among whom 16 *LMNA*–mutated lipodystrophies (LDM), *16* non-*LMNA* mutated partial lipodystrophies (LDNM), and 20 other types of lipodystrophies), 28 obese (O; 12 diabetic (OD) and 16 non-diabetic (OND)) and 14 normal-weighed healthy subjects (C). The anthropometric (DEXA, MRI) characteristics and leptin levels of the patients were recorded. Three ratios were calculated to assess the respective part of fat and lean mass (FM/LM), intra- and whole abdominal fat (IAF/WAF) and adipose tissue function (leptin/WAF).
Results
The three groups differed by the FM, LM, IAF, WAF, leptinemia, trunk FM/LM ($P < 0.0001$), IAF/WAF ($P < 0.001$) and leptin/WAF ($P < 0.01$). The main distinctive feature of LDM compared to C was IAF (188 ± 38 *vs* 82 ± 23 cc; $P < 0.01$) whereas BMI, FM, LM, WAF and leptinemia were similar. The ratios ranges of the five subgroups were as follows: IAF/WAF: 0.5 in LDM *vs* 0.3 in all other subgroups; trunk FM/LM: 0.2 in LDM and C, increased from 0.5 to 0.7 and 0.8 respectively in LDNM, OD, OND); leptin/WAF: decreased to 2.3 and 1.6 in respectively LDM and LDNM compared to C (2.7), and increased in OD (3.7) and OND (5.6).
Conclusion
Increased intra/whole abdominal fat ratio, hypoleptinemia and preserved fat/lean mass ratio characterized lipodystrophic laminopathies, in contrast with obese people who showed an increased fat/muscle mass, hyperleptinemia and preserved intra/whole abdominal fat ratio. Non-mutated lipodystrophic patients were intermediate, with decreased leptin/WAF ratio, close to LDM, and increased IAF/WAF and FM/LM ratios close to the obese population.

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Pituitary Basic

OC12.1

Human AIP gene rescue lethality in a *Drosophila melanogaster* knockout model of AIP orthologue

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Introduction
Heterozygote loss-of-function mutations in AIP (Aryl hydrocarbon receptor interacting protein) predispose to young-onset pituitary adenomas. Homozygote murine knockout model of AIP leads to lethality. While the majority of the 75 published AIP mutations result in truncated or missing proteins, missense mutations are more difficult to characterise and to establish their pathogenic role. We have identified the orthologue of AIP, CG1847, in Drosophila melanogaster. This protein has high level of homology with human AIP.
Methods
We generated a *CG1847* deficiency *via* RNAi knockdown (using two different RNAi-lines) or *via* knocking out two of the three exons of *CG1847* by imprecise excision of a transposable P-element located in the 5′-UTR of *CG1847.*
To functionally test the homology between human *AIP* and *CG1847,* a UAS::humanAIP construct was made by inserting the human *AIP* coding sequence, downstream of the GAL4-dependent UAS promoter into the *pUASK10attB* vector. Microinjection of this construct into fruitfly embryos harbouring attP40 landing sites enabled us to obtain transgenic fruitflies with human AIP sequence on the second chromosome balanced over CyO. We tested whether this UAS::humanAIP transgene was able to rescue $CG1847^{exon1\_2}$ mutants by expressing it with a ubiquitous driver during fly development.
Results
Our data show that both in the knockdown and knockout of *CG1847* results in lethality in the fruitfly. Strikingly, we found that human *AIP* gene can rescue the lethality of *Drosophila melanogaster* knockout model of AIP orthologue, demonstrating that CG1847 is the functional homolog of AIP.
Conclusions
We are able to rescue the lethality of fruitfly $CG1847^{exon1\_2}$ mutant with human *AIP*, confirming that *CG1847* is a highly conserved gene throughout evolution. This system can be used to test human *AIP* missense variants, where pathogenicity cannot be easily determined based on clinical data.
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OC12.2

Differential *in vitro* response to octreotide and pasireotide in normal and tumoral primary pituitary cell cultures

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Somatostatin analogs (SSA) are a first-line treatment for pituitary adenomas (PA). Indeed, multi-receptor targeting SSA such as octreotide and pasireotide are being successfully used to control hormone secretion and/or tumor growth. Unfortunately, many PA escape from SSA-therapy, which could be related to somatostatin receptor (sst) presence, abundance, availability and/or signaling. In order to better define the molecular/cellular features associated to octreotide and pasireotide responsiveness, we have established a reliable methodology to evaluate, in parallel, the *in vitro* response to octreotide and pasireotide using primary PA cultures by assessing sst-signaling (free-cytosolic (Ca^{2+}) kinetics) and secretory and proliferative responses. In addition, expression of pituitary hormones and ssts using RT-PCR and, hormonal secretion by immuno-blotting was assessed. A total of 44 samples (16 somatotropinomas, 6 corticotropinomas, 5 prolactinomas, 15 non-functioning PA (NFPA) and 2 normal pituitaries) were evaluated. Octreotide and pasireotide treatment decrease (Ca^{2+}) kinetics in 13/16 and 7/16 somatotropinomas respectively; while both SSA similarly inhibited GH secretion and proliferation. Inhibition of (Ca^{2+}) kinetics in response to octreotide and pasireotide were observed in 2/6 and 4/6 corticotropinomas, although it only occurs in a small proportion of cells, whereas ACTH release was not significantly affected. In prolactinomas, only octreotide inhibited (Ca^{2+}) kinetics. In NFPA, both SSA moderately decreased (Ca^{2+}) kinetics (few responsive PA, with moderate inhibition and small proportion of responsive cells), while surprisingly, both SSA stimulated cell proliferation in a considerable proportion of PA. Finally, octreotide did not alter (Ca^{2+}) kinetics in normal pituitary cultures while, pasireotide exerted a faint inhibitory response. The differential response to octreotide and/or pasireotide could not be explained by significant differences in sst-expression pattern between responsive and non-responsive PA. Altogether, our data indicate the existence of a differential *in vitro*response to octreotide and pasireotide in normal and tumoral primary pituitary cell cultures and therefore, further studies are necessary to unveil the key factors involved in this differential responsiveness to SSA.

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OC12.3

Detection of pituitary antibodies by immunofluorescence: Methodological approach and results in patients with pituitary diseases

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Pituitary antibodies have been measured mainly to identify patients whose disease is caused or sustained by pituitary-specific autoimmunity. Although reported in over 100 publications, this antibody test has variable results and limited clinical utility. Our goals were to: identify major sources of variability; test them experimentally for establishing an optimized immunofluorescence protocol; assess prevalence and significance of pituitary antibodies in patients with pituitary diseases. We first evaluated the effect of pituitary gland species, section fixation, autofluorescence quenching, blockade of unwanted antibody binding, and use of purified immunoglobulins G on the performance of this antibody assay. We then measured cross-sectionally the prevalence of pituitary antibodies in 390 pituitary cases and 60 healthy controls, expressing results as present or absent and according to the (granular, diffuse, perinuclear, or mixed) staining pattern. Human pituitary was the best substrate to detect pituitary antibodies, and yielded an optimal signal-to-noise ratio when treated with Sudan black B to reduce autofluorescence. Pituitary antibodies were more common in cases (95 of 390, 24%) than controls (3 of 60, 5%, $P=0.001$) but did not discriminate among pituitary diseases when reported dichotomously. On the contrary, when expressed according to their cytosolic staining, a granular pattern was highly predictive of pituitary autoimmunity ($P<0.0001$). This study reports a comprehensive study of pituitary antibodies by immunofluorescence and provides a method and an interpretation scheme that should be useful for identifying and monitoring patients with pituitary autoimmunity.

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OC12.4

Identification and characterization of pituitary adenoma stem-like cells in human non functioning pituitary adenomas

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Several studies support the existence of multipotent stem/progenitor cells in the adult pituitary, whereas the presence of stem cell in pituitary tumors and their role in pituitary tumorigenesis are still on debate. Aim of this study was to identify and characterize stem-like cells in non-functioning pituitary adenomas (NFPAs). To this purpose primary cell cultures from 25 NFPAs were grown in culture conditions that favored stem cell growth (EGF, bFGF and B27 containing medium). The expression of stem cell markers and genes involved in pituitary development was evaluated after 3 weeks of culture by FACS analysis, RT-PCR and immunofluorescence.

We successfully isolated sphere-forming cells from 64% of NFPAs tested (16/25). These cells expressed stem cells associated markers CD90 and CD34, with a proportion of CD90+ and CD34+ cell populations variable between different tumour samples, ranging from 2.7% to 13.5% for CD90+ and from 1.1% to 10.4% for CD34+. Moreover, RT-PCR analysis revealed the expression of stem cell markers Sox2, Oct4, Nanog, Dkk1 and Egr1, transcription factors involved in gonadotroph differentiation (DAX1, SF1) and the glycoprotein hormone alpha subunit (alphaGSU), consistent with gonadotroph lineage derivation of most NFPAs.

By immunofluorescence analysis, we showed that these sphere-forming cells are Nestin+ and coexpress Sox2 with E-cadherin and the pituitary embrionic factor Prop1.

Since some of these spheres expressed also somatostatin (SS) receptor 2 (SST2), we test a possible effects of SS analog octreotide on spheres growth. We found that octreotide treatment reduced the number of sphere-forming cells after 30 days of cell culture in stem cell-permissive medium (about -50% vs untreated cells).

In conclusion, our data demonstrate the existence in a good proportion of NFPAs of stem-like cells, that expressed stem cell-associated markers and pituitary embryonic factors. Further experiment are needed to test long-term self-renewal and multipotency of these cells.

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OC12.5

Does hypercortisolism of Cushing's syndrome affect telomere length?

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Introduction

Hypercortisolism in Cushing's syndrome (CS) determines increased mortality and morbidity. Hypercortisolism is also present in chronic depressive disorders and stress, where telomere length (TL) is shorter than in controls. We hypothesized that telomere shortening may occur and contribute to premature morbidity in CS.

Aim

Investigate TL in CS compared to matched controls, and longitudinally in a subset of CS patients evaluated both with active disease and after endocrine cure.

Methods

Seventy-seven CS patients (14 males, 59 of pituitary and 17 of adrenal origin; 21 with active disease) and 77 matched controls (for age, gender, smoking) were compared. Mean age was 48 ± 12 in CS *vs* 48 ± 12 years in controls. In 15 active

patients, a second analysis was also performed once they were in remission (mean age 43 ± 12 *vs* 46 ± 11 years, respectively, $P < 0.05$). Leukocyte TL was measured by TRF-Southern technique (kit-telo TTAGGG Telomere length Assay, Roche).

Results

A negative correlation between TL and age was found ($r -0.341$, $P < 0.001$). CS patients had more hypertension, diabetes, dyslipidemia, osteoporosis, a greater BMI and total leukocyte count in CS than controls ($P < 0.05$). Globally, mean TL did not differ in CS and controls (7667 *vs* 7483 base pairs-bp-). TL shortening was observed in both CS and controls with dyslipidemia (controls 7213 *vs* 7700 bp and CS 7328 *vs* 7957, $P < 0.05$). After adjustment for age, TL was shorter in active disease than in remission (7271 *vs* 7870, $P < 0.05$).

Conclusions

As previously described, aging and dyslipidemia were associated with TL shortening in both CS and controls, but did not differ globally. However, we show for the first time that when patients are followed longitudinally, active CS is associated to TL shortening compared to remission, suggesting a negative impact of hypercortisolism on the telomere maintenance system.

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Nurse Posters

N1

Level of knowledge about type I diabetes mellitus among nurses employed at endocrinological dispensaries

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The work was initiated to assess basic level of knowledge on essential concepts of type I diabetes mellitus among nurses employed at regional dispensaries of Uzbekistan.
We tested 194 nurses employed at the endocrinologist's offices and regional endocrinological dispensaries to assess level of knowledge on essential concepts of type I diabetes mellitus by means of a 20 question test made up under a 5-day training program in the School of Diabetes.
The testing demonstrated that initial basic level of knowledge among nurses in Uzbekistan as a whole was 65%, the highest one being registered in Tashkent (83%), the lowest one in Djizak (55%), Bukhara (58%) and Khorezm (58%) regions. Analyzing answers to each question we found that there were 91.8% of right answers to questions about distinguishing features of type I and type II diabetes mellitus, 89% of respondents gave right answers to question about changes in blood glucose upon insulin deficiency to indicate not bad level of knowledge on these concepts in Uzbekistan as a whole. 70% of nurses knew a thing or two about glucagon. 56% chose right answer to a question about substances (proteins, fats or carbohydrates) facilitating increase of blood glucose. 54% of respondents knew about renal threshold of glucose. 82% of nurses knew normal values of glycemia. Only 57% of respondents had a good command of type I DM criteria of compensation in children and adolescents. 42% of respondents gave right answers to questions about value of measurement of glycated hemoglobin. Enquiry after training demonstrated the best results in Navoyi, Surkhandarya, Tashkent, Kashkadarya and Samarkand regions where right answers were given to 95–100% of questions. The lowest level of knowledge was found in Djizak, Bukhara and Khorezm regions indicating necessity of the repeated training and build-up of control over the regions.
The tested nurses were found not to have adequate knowledge about clinical picture and pathogenesis of diabetes mellitus, misapprehending first-aid treatment upon acute complications and having a vague idea about insulin injection technique. Constant monitoring of a diabetic self-control should be performed by all health care professionals contacting with the patients.

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N2

Radiation-induced multiple late complications after childhood acute lymphoblastic leukemia: A case report

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Introduction
Acute lymphoblastic leukaemia (ALL) is the most common childhood malignancy and accounts for 25% of all childhood cancer. With dramatically improved survival rates the long term treatment complications are very important. ALL patients treated with cranial radiotherapy (CRT) and chemotherapy are at increased risk of GH deficiency (GHD), hyperparathyroidism, thyroid cancer and meningiomas.
Method
We present a 45-year-old woman diagnosed with ALL at age 4 years and treated with prophylactic cranial-spinal radiotherapy of 24 Gy and chemotherapy. The patient was diagnosed with GHD at age 32 years. At present she has been treated with GH during 13 years with a median dose of 0.3 mg/day.
Result
She is now menopausal, osteopenic (lumbar spine; *Z*-score −1.3 S.D.) and femoral neck; *Z*-score −1.0 S.D.), has primary hyperparathyreoidism, thyroid nodules with papillary microcancer, and on MRI 3 meningeomas and one cavernoma is shown. After surgery of one parathyroid adenoma and thyroidectomy of the left thyroid lobe the postoperative levels of PTH and Calcium returned to normal levels. The findings in CNS will be followed with regularly MRI scans.
Conclusion
This typical ALL case shows the spectrum of possible late complications after treatment for childhood ALL that may involve the entire endocrine system. The latency period is variable and the clinicians must have a high index of suspicion. We estimate that 500 ALL patients are at risk in Sweden (9 million) with the corresponding numbers in other countries.

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N3

Reduced psychological mental stress improved glycemic control in type 2 diabetic patients.

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Psychological mental stress is associated with poor glycemic control in type 2 diabetes mellitus. The aim of this study is to exam the effect of psychological mental stress on glycemic control during short-term admission for diabetic educational program in type 2 diabetic patients. This study was carried out in 18 type 2 diabetic patients aged 44–82 years who were shortly admitted for diabetic educational program in our hospital. We measured salivary alpha-amylase activity for the marker of psychological mental stress using a portable analyzer at first and last days in educational hospitalization and then patients were divided into two groups, including one group was to decrease salivary alpha-amylase activity in before and after measurement (named stress-improved group), the other group was to increase (named stress-worsened group). Moreover, health-related quality of life was evaluated using the 36-item Short Form (SF-36) version 2 questionnaire. The SF-36 is divided into eight categories: physical functioning, role limitation due to physical health, bodily pain, general health, vitality, social functioning, role limitation due to emotional health, and mental health. These scales are scored from 0–100, with higher scores indicating better states of health and quality of life. After measurement of salivary alpha-amylase activity, there were nine patients in stress-improved group and nine patients in stress-worsened group. There were no significant baseline differences between the two groups, e.g., age, duration of diabetes mellitus, body mass index and average glycosylated hemoglobin (HbA1c). However, HbA1c at 3 month after discharge was pivotally decreased in stress-improved group as compared with in stress-worsened group. Furthermore, SF-36 analysis showed that the scores of social functioning and mental health were significantly high in stress-improved group as compared with in stress-worsened group. In conclusion, it was suggested that the psychological approach but also medication was required for glycemic control in type 2 diabetic patients, possibly indicating that co-medical staff such as nurses should also develop those approaches to diminish psychological mental stress.

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N4

Adherence to treatment for chronic hypogonadism: the role of illness perceptions and depressive symptoms

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Background
For chronic diseases, adherence to treatment remains a major clinical challenge. For men with long-term hypogonadism, there is scant data regarding adherence to treatment. Congenital hypogonadotropic hypogonadism (CHH) is a rare, genetic, endocrine disorder characterized by incomplete/absent puberty and infertility. Little is known about adherence in this patient population or the psychosocial implications of living with this rare disorder. Therefore, we aimed to evaluate illness perceptions, depressive symptoms, and patterns of adherence to treatment in men with CHH.
Methods
An online, web-based patient survey was used to examine how patients perceive CHH (Revised Illness Perception Questionnaire), assess their depressive symptoms (Zung Self-Rating Depression Scale), and measure their treatment adherence (Morisky Medication Adherence Scale). Comparisons were made to normative reference populations and other chronic endocrine disorders (Cushing's and acromegaly).
Results
83 CHH men completed the survey and reported often lengthy gaps in treatment (27% with pauses >1 year) and discontinuity of care (41% without healthcare >1 year). These men exhibit significantly increased rates of mild (subclinical),

moderate, and severe depression compared to controls (all $P<0.001$). Patients suffer significant physical, psychological and social consequences as a result of CHH and the negative emotional impact of having CHH is correlated with depressive symptoms ($P<0.001$). Poor medication adherence was associated with more perceived negative consequences and more depression symptoms (both $P<0.05$). Higher illness coherence (making sense of CHH) appeared to be a protecting factor for depressive symptoms ($P<0.001$).
Conclusions
CHH patients report significant psychosocial burdens that are associated with gaps and discontinuity in care. These data highlight the importance of examining the psychological and emotional impact of living with a chronic condition as these factors can affect adherence to treatment and subsequent morbidity (i.e. metabolic and skeletal health sequelae). A follow-up study is currently underway to identify specific targets for patient-centered e-health interventions to promote better health outcomes and enhanced quality of life in these dispersed patients.

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N5

Acromegaly patients' experiences of nursing

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In 2007 a qualitative study of 36 patients' observations of diseases, care and life disorders associated with Acromegaly was conducted. Inclusion and exclusion criteria are described. The sample cuts across both gender and age. Seven patients didn't want to participate. The reason for this is only known for some of them. A literature search in a pilot study of nine patients revealed that this patient group was qualitative unexplored. Research interviews were conducted at the control hospitalization. The Data Protection Agency approved the project, and the patients were informed of the rules for participation. An Interview guide was used, and interviews were conducted until data saturation was achieved. Interviews were recorded, and transcription was performed by the researcher.
The patients' statements were categorized by Eriksson's disease, care and life disorders and the three operational levels from Kvale's analysis model were used.
The research project's most spectacular findings were that:
i) The patients didn't experience that caregivers had knowledge of the disease and symptoms
ii) Other patients with Acromegaly were an important source of information
iii) Being a teaching object for junior doctors was informative educational.
Subsequently various initiatives were undertaken to optimize nursing. Among other things, hiring a specialist chief nurse, an informative theme evening for the staff, preparation of a short-term record for documentation, endocrinology training program, and in 2011 a quantitative survey of 20 patients was completed. Patients' experiences of nursing in the control admissions were in focus. The inclusion criterion was that the patients had followed the control admissions since 2005. The results were: a greater satisfaction with call letter, receipt and hospitalization, a significant positive change in nursing since 2007, and the staff showed greater interest and commitment. However, there is still room for improvement as to daily discomfort.

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N6

Effects of *PRKAR1A* mutations in behavior and brain function

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Background
Various genetic syndromes have identified distinct and consistent behavior patterns. Carney complex (CNC) is a rare multiple endocrine neoplasia syndrome first described by Dr Carney in 1985 as a complex of myxomas (cardiac, skin), spotty skin pigmentation, and endocrine over activity. CNC is caused by mutations of the *PRKARIA* gene that encodes the RIα regulatory subunit of Protein kinase A (PKA). We recently reported that a *Prkar1a* heterozygote mouse that was developed in our lab showed brain region-specific increased PKA activity that was associated with anxiety-like behavioral phenotype. We investigated the behavioral and clinical phenotype of adults and children with CNC.
Methods
Chart review of 56 adults and 50 children evaluated on CNC protocol.
Results
Sixty-seven percent of adults with *PRKAR1A* mutations were diagnosed with a psychiatric disorder compared to 29% of adults with clinical features of CNC who were negative for *PRKAR1A* mutation ($P<0.01$). Fourty-three percent of pediatric patients with *PRKAR1A* mutations were diagnosed with a psychiatric disorder compared to 11% of children with clinical features of CNC who were negative for *PRKAR1A* mutation ($P<0.02$). The most frequent psychiatric diagnosis in adults with *PRKAR1A* mutation were: anxiety, depression, and bipolar disorder (in that order), while for children with *PKKAR1A* mutation were: learning difficulties, attention deficit hyperactivity disorder, anxiety, and depression (in that order). For adults, *PRKAR1A* mutation was associated with a higher clinical severity score (CSS) ($P<0.01$), but there was no correlation between CSS and a diagnosis of psychiatric disorder.
Clinical Implications
Somatization is common with chronic illness. Behavioral patterns associated with known genetic alterations are useful to provide anticipatory guidance from an educational, rehabilitative, and parenting perspective. It appears that PRKAR1A inhibition in humans and *Prkar1a*-down-regulation in mice is associated with increased risk for psychopathology, consistent with the importance of this protein in cAMP/PKA signaling in brain function.

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N7

The Nordic network for endocrine nurses (NNEN).

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Background
Previously, the endocrine nurses in Sweden, Denmark, Norway, Finland and Iceland have not been organized. As Endocrine nursing is specialized and no education for a specialist competence in endocrinology is available there is a need for a collaboration to improve the Nordic endocrine nursing.
Purpose
The purpose of the Nordic network for endocrine nurses (NNEN) is to enhance the Nordic endocrine nurse knowledge and skills, and also work for a specialist competence in endocrinology.
Methods
NNEN was initiated in year 2011 as a volunteer network with the objective of organizing Nordic endocrine nurses. Currently, NNEN has 110 members including a working group consisting of 8 nurses actively working for the main goal, to initiate a specialist competence in endocrinology. Membership is free.
Results
NNEN is organizing annual meetings with the aim to educate and promote professional development of endocrine nurses. NNEN serves as a platform to share expertise and experience in nursing, as well as promoting members to attend international meetings. NNEN also promotecollaboration between health professionals with the nurse as a key member of a multidisciplinary health care team and advanced nurse-led service to provide the patients with high quality care by offering an effective, safe and person centered care.
In 2014 we are also planning to starta two dayeducation in endocrinology. We aim to have these courses annual and to conduct them regionally so as many members as possible can participate.
Conclusion
NNEN enables us to share knowledge and provide us with a tool towards evidence based care offered to patients with endocrine diseases. NNEN also promotes the professional development of endocrine nurses role with the aim of offering patients an effective, safe and person centered care advancing the nurse as a key member of a multidisciplinary health care team.

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N8

Application of international classification of functioning, disability and health to assess physical function in patients with diabetes Mellitus

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The international classification of functioning, disability and health, known more commonly as ICF, is a classification of health and health-related domains. These domains are classified from body, individual and societal perspectives by means of two lists: a list of body functions and structure, and a list of domains of activity and participation. Since an individual's functioning and disability occurs in a context, the ICF also includes a list of environmental factors.

The aim of the study was application ICF to evaluate physical functioning of patients with diabetes mellitus (DM).

Total number of domains available in the full version of the ICF is 1424. A development of brief set of domains that characterize profile of functioning of patients with DM was first stage of the study.

A basis for developing a brief set of domains that characterize the profile of functioning of the patients with diabetes, we used a set, previously developed by experts from WHO (2003), expanding and adapting it. We changed the proposed sets of domains to adapt the set of domains and to facilitate their evaluation, leaving the most significant and deleting domains that are difficult to objectification and irrelevant for peer review.

The next stage of the study was to develop criteria for assessing deviation or loss of functions and structures, activity limitations and opportunities for participation, the degree of positive or negative influence of context factors in patients with type 2 DM, from the standpoint of the ICF.

All three components are classified in the ICF (body functions and structures, activities and participation, and environmental factors) were measured using a single rating scale. Depending on the component, the existence of the problem meant a violation, limitation or restriction of opportunities obstacle. Relevant determinants were chosen to each domain of classification.

Using the developed method you can make an individual profile of the physical functioning of patient. We recommend using this method in medical examination and medical rehabilitation.

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Poster Presentations

Adrenal cortex

P1

Which serum cortisol after high dose short synacthen test, 30 or 60 min?

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Background
Short synacthen(cosyntropin)test, has replaced the insulin stress test as the first-line test to assess adrenal insufficiency. The aim of this study, was to determine the utility of the 30 and 60 min cortisol measurement in the high dose (250 μg) short synacthen test.
Methods
Cross sectional study was conducted by reviewing the database of patients underwent short synacthen test in Al-Faiha Diabetes Endocrine and Metabolism Center (FDEMC) for the peroid from November 2009 to May 2013.
Results
Study participants includes 435 patients. The cortisol response in short synacthen test was sufficient in 198 (45.5%) patients, and abnormal in 237 (54.4%) patients. It was insufficient at 30 min only in 56 (12.9%) patients, insufficient at 60 min only in 5 (1.1%) patients and insufficient at both 30 and 60 min in 176 (40.5%) patients. Insufficient at 30 min and sufficient at 60 min was seen in 120 (27.6%) patients. This means that the false negative test if the 60 min sample was not taken was 27.6%. Only 5 (1.1%) patients with normal response at 30 min will regress to response at 60 min.
Conclusion
Measuring both 30 and 60 min cortisol level are necessary and at 60 min is fundamental in interpretation of short synacthen test.

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P2

Development of new improved derivatives of iodometomidate for the diagnosis of adrenocortical tumours and radiotherapy of adrenal carcinoma

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Objective
We have developed ($^{123/131}$I)iodometomidate (IMTO) for specific adrenal imaging and radiotherapy of adrenocortical carcinoma. IMTO binds with high affinity and specificity to the two adrenocortical enzymes aldosterone synthase (CYP11B2) and 11β-hydroxylase (CYP11B1). Metabolic analysis has revealed very rapid metabolization of IMTO both *in vitro* and *in vivo* by hepatic esterases. Due to the low metabolic stability of ($^{123/131}$)IMTO we have developed new stabilised radiotracers in order to improve specificity and therapeutic efficacy.
Methods
We have developed more than 90 IMTO derivates in which the metabolic labile methyl esters were replaced by other esters, amides, or bioisosteres, respectively. The inhibition of aldosterone/cortisol was tested in murine Y1 cells expressing human CYP11B1/CYP11B2. Radiosynthesis of the 16 compounds with the highest affinity to both enzymes was established and stability was determined by radio-HPLC after coincubation with liver microsomes. In addition, intracellular uptake was determined in human adrenocortical NCI-H295 cells and biodistribution in male CD1 mice was analyzed.
Results
16 IMTO analogues especially the aliphatic esters and tertiary amides showed comparable or better enzyme binding than IMTO. These new radiotracers showed also high specific intracellular accumulation comparable to the reference substance ($^{123/131}$I)IMTO in NCI-H295 cells. In animal experiments particularly the amides showed an extremely high and impressively specific uptake in the adrenal gland. One candidate showed a tenfold higher uptake than (^{125}I)IMTO in the adrenal gland of CD1 mice 240 min after injection and $<1\%$ ID/g tissue in all other organs.
Conclusion
We have successfully developed many new radiotracers with comparable or even better binding properties and superior metabolic stability than ($^{123/131}$I) iodometomidate. These compounds may be suitable for nuclear medicinal diagnostic and radiotherapy of adrenocortical carcinoma.

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P3

Cardiovascular risk in Cushing's syndrome vs obesity

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Introduction
Cushing's syndrome (CS) is associated with central obesity, hypertension, insulin resistance, dyslipidemia, prothrombotic state, manifestations which form a metabolic syndrome. Accelerated vascular senescence, due to metabolic and vascular changes, increases, in CS, the cardiovascular risk and the mortality rates compared to age- and gender-matched population. On the other hand, obesity itself is associated with numerous comorbidities, including hypertension, diabetes mellitus, dyslipidemia and major cardiovascular diseases.
Aim
To evaluate the prevalence of the cardiometabolic complications and the cardiovascular risk in CS compared to obese patients.
Methods
43 patients, mean age 41.46 ± 6.11 years, 39 (90.6%) females, with endogenous CS (26 with Cushing's disease and 17 with adrenal Cushing's) and 50 age- and gender- matched subjects with obesity were retrospectively analyzed.
Results
Mean BMI was significantly higher in obese patients than in patients with CS (39.54 ± 3.99 vs 32.26 ± 7.41 kg/m^2, $P<0.001$). Systolic blood pressure (139.05 ± 20.74 vs 130.2 ± 19.61 mmHg, $P=0.045$), diastolic blood pressure (87.77 ± 13.06 vs 79.59 ± 10.59 mmHg, $P=0.002$) and blood glucose levels (106.94 ± 28.95 vs 93.38 ± 13.69 mg/dl, $P=0.005$) were higher in CS patients than in obese patients. The prevalence of hypertension (62.5 vs 34%, $P=0.007$, $\chi^2=7.25$), coronary heart disease (20.5% vs 6%, $P=0.039$, $\chi^2=4.26$), diabetes mellitus (32.6% vs 10%, $P=0.03$, $\chi^2=8.75$) and metabolic syndrome (NCEP ATP III criteria) (64.4% vs 40.8%, $P=0.032$, $\chi^2=4.58$) was higher in CS patients compared to obese patients. The 10 years cardiovascular risk (Framingham risk score) was almost double in CS patients compared to obese subjects (9.02% vs 4.66, $P=0.006$), the risk being higher in patients with adrenal CS compared to patients with Cushing's disease (12.47 vs 5.59, $P=0.015$).
Conclusion
Our study reveals a higher prevalence of cardiometabolic complications and an increased cardiovascular risk in patients with Cushing's syndrome compared to obese patients, the risk being higher in patients with adrenal CS than in patients with Cushing's disease.

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P4

ACTH-secreting pheochromocytoma: case report

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Introduction
We report the clinical presentation of pheochromocytoma with Cushing's syndrome due to ectopic production of ACTH, and assess the histopathological diagnosis, treatment modality and prognostic factors compared with the literature.
Results
Cushing's Syndrome due to ectopic ACTH production is uncommon and due to pheochromocytoma is extremely rare. We discuss the case of a 50-year-old female who initially presented with vague, non-specific symptoms, such as general and muscle weakness, weight loss, body temperature rise, high blood pressure, increase in fasting blood glucose, in which an ACTH-secreting tumor

found to be the cause of her clinical presentation. At admission: height 168 cm, weight 57 kg. asthenic constitution, diffusely hyperpigmented skin, 'darkened elbow' symptom, and subcutaneous adipose tissue was insufficiently developed. Laboratory showed AM cortisol of 1488 mmol/l, PM cortisol of 1672 mmol/l, 24 h urinary free cortisol of 3700 nmol/day, AM ACTH level of 178.7 mg /ml, PM ACTH level of 1798 mg /ml and non-suppression of cortisol with overnight dexamethasone suppression test (1 and 8 mg). 24 h urinary level of normetanephrine and metanephrine: normetanephrine – 830 mg/day, metanephrine – 1481 mg/day. Brain MRI showed no pathological changes. CT scan showed tumor of the left adrenal gland (2.7×3, 0×4, 6 cm, density 38H). She underwent 3 weeks therapy by doxazozine and mifepristone before surgery. So, clinical and laboratory signs of Cushing's syndrome and pheocromocytoma disappeared after left adrenalectomy.

Conclusion

Despite numerous guidelines in pheochromocytoma and Cushing's syndrome, there are still diagnosis and treatment mistakes due to rarity and complexity of clinical presentation in ACTH-ectopic syndrome caused by pheocromocytoma. So, we need to improve the guidelines for diagnosis and treatment of ACTH-ectopic tumors.

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P5

Are small adrenal incidentalomas solely a radiological finding?

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Introduction

The criteria defining the threshold size of adrenal incidentaloma (AI) are >1 cm diameter. However, data about AI ≤1 cm diameter is scant. The aim of this study is to evaluate function of adrenal masses ≤1 cm and to compare them with adrenal masses >1 cm as well as to understand the possible utility of determining salivary cortisol in diagnosis of SCS in patients with AI.

Method

The study included 137 consecutive patients with AI (38 and 99 AI at ≤1 and >1 respectively).

Results

SCS was 5.3 and 17.2% in AI ≤1 cm and >1 m diameter, respectively. The patients with >1 cm AI had a higher prevalence of SCS and primary hyperaldosteronism than patients with >1 cm AI did, but they did not differ significantly. The prevalence of diabetes and hypertension was high both in non-functional AI with ≤1 and >1 patients and showed no significant difference between two groups. Using a cut-off of 0.33 μg/dl for midnight salivary cortisol (MNSC), sensitivity, specificity, values of positive and negative predictivity for diagnosis of SCS were 58, 86, 40.7 and 91.8% respectively.

Conclusion

The AI ≤1 cm harboured SCS as was the case in AI >1 cm. Similar to AI >1 cm, non-functional AI ≤1 cm also had higher prevalence of diabetes and hypertension. Furthermore, MNSC in patients with AI was found comparable with midnight serum cortisol in diagnoses of SCS.

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P6

An autopsy case of ectopic ACTH-secreting lung carcinoid with Cushing's syndrome

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A 81-year-old woman came to our hospital with complaints of reduction in appetite and weakness of lower limbs. She had developed Cushing's features. Initial laboratory evaluation revealed severe hypokalemia and hyperglycemia without ketoacidosis, and diabetes mellitus had not been detected previously. A series of hormonal assessment revealed marked ACTH-dependent hypercortisolism. Corticotrophin-releasing hormone stimulation test resulted in normal ACTH response, thus we ran additional tests to make a diagnosis of Cushing's disease. However, magnetic resonance imaging showed no obvious tumor in her hypophysis. Furthermore, whole-body computed tomography and positron emission computed tomography did not identify apparent tumor. Therefore, we diagnosed it as occult ectopic ACTH-secreting tumor, so we administered octreotide acetate 20 mg/4 weeks and trilostane 240 mg/day. After this treatment, hormonal level had been slightly improved. However, she had been compromised and had experienced recurrent infections, for example, pneumonia and infectious spondylitis. Finally, she was admitted to our department for inflammation of the bile duct. She developed septic shock and dis-seminated intravascular coagulation. Although we started antibiotic, vasopressor and lyophilized human antithrombin? concentrate, she deteriorated rapidly and died 2 day later. Autopsy was performed and showed a solitary adrenal corticotropic hormone-producing neuroendocrine tumor in the right lung, which was 17 mm in diameter. This tumor was stained by CD56, chromogranin a and synaptophysin, so we diagnosed ectopic adrenocorticotropic hormone secreting lung carcinoid. We experienced a case that we could not detect a localization of ACTH-secreting tumor regardless of repeated radiological imaging, but autopsy confirmed its diagnosis.

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P7

Favorable long-term outcome of bilateral adrenalectomy in Cushing's disease

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Objective

Bilateral adrenalectomy (BADX) is an important treatment option for patients with Cushing's syndrome (CS). The outcome of this procedure has not been studied well.

The aim was to analyze long-term outcome of CS patients treated with BADX.

Design

Fifty patients with BADX treated since 1990 in two German centers were identified. 34 patients had Cushing's disease (CD), nine ectopic Cushing-syndrome (ECS), and seven ACTH-independent bilateral adrenal hyperplasia (BAH).

Methods

Standardized follow-up examination was performed in 36 patients with a minimum follow-up time after BADX of 6 months and a median follow-up time of 11 years. Surgical, biochemical and clinical outcome as well as morbidity and mortality were studied.

Results

Surgical morbidity and mortality were 6 and 4%, respectively. All patients went in remission after BADX. Nearly all Cushing's specific comorbidities except for psychiatric diseases improved significantly. Health related quality of life remained impaired in 45.0% of the female and 16.7% of the male patients compared to healthy population. Median number of adrenal crises per 100 patient-years was four. Nelson tumor occurred in 24% of CD patients after a median time span of 51 months. Long-term mortality after 10 years was high in ECS (44%) compared to CD (3%) and BAH (14%).

Conclusions

BADX is an effective and relatively safe treatment option especially in patients with CD. The majority of patients experience considerable improvement of Cushing's symptoms.

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P8

Analysis of BclI, N363S and ER22/23EK polymorphism of the glucocorticoid receptor gene in a large series of patients with adrenal incidentaloma

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Introduction
Some variants of the glucocorticoid receptor (GR) gene have been found to alter glucocorticoid sensitivity and have been associated with worsen metabolic profiles.
Objective
The aims of the present study were: i) to examine whether the prevalence of N363S, ER22/23EK and BclI variants was different in patients with adrenal incidentaloma (AI) and/or subclinical Cushing's syndrome (SCS) than control subjects and ii) whether the presence of these gene variants may be linked to metabolic or hormonal abnormalities in patients with adrenal incidentalomas or subclincal Cushing's syndrome.
Methods
The study included 411 patients with adrenal incidentalomas and 189 control subjects. Metabolic and hormonal parameters and GR gene variants (on genomic DNA by pyrosequencing assays) were determined.
Results
When compared with control subjects, the carrier frequency for the three variants was similar (N363S 5.4 vs 9.1%, BclI 54 vs 44.6%, ER22/23EK 4.4 vs 3.8%) and we have not observed any difference between patients with SCS and non-secreting adenoma.
In a multiple regression analysis in patients with DST <1.8 μg/dl the N363S variant seems to be an independent predictor of hypertension ($P=0.015$).
Conclusion
We have not found any difference in the prevalence of the evaluated SNPs between patients and controls. The ER22/23EK and BclI variants don't seem to have any influence on hormonal secretion and clinical presentation. N363S could influence blood pressure levels. However, the effect seems to be more evident in patients with normal cortisol secretion, while it is less apparent in subjects with an autonomous cortisol secretion. It should be hypothesized that cortisol secretion outweighs the effect of GC receptor sensitivity on clinical phenotype.

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P9

Hormonal and clinical correlations in nonfunctional adrenal incidentalomas

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Introduction
The prevalence of incidentally found adrenal tumors – adrenal incidentalomas (AI) – in imaging procedures and autopsy series is up to 4.5–8.7%. Endocrine and clinical evaluation is carried out to diagnose hormonal function or malignancy of the tumors. Nonfunctional adenomas comprise about 80% of AI. The aim of the study was to identify possible association between various clinical, hormonal and radiological features of nonfunctional AI.
Methods/design
We enrolled 100 patients aged 20–70 years with adrenal tumors discovered incidentally in computed tomography after ruling out possible hormonal function and radiological features of malignancy. We analyzed concentrations of many adrenal hormones. Overnight dexamethasone suppression test (DXM) was performed in the whole group and ACTH (Synacthen) stimulation test in 38 random subjects.
Results
The group consisted of 71% women and 29% men, 26% bilateral and 74% unilateral tumors. Prevalence of obesity, hypertension and diabetes were 32, 56 and 13% respectively. In bilateral tumors mean ACTH, DHEAS, basal 17-OH-progesterone (17OHP) were lower and DXM and stimulated 17OHP were higher than in unilateral lesions. There was a positive correlation between tumor size and DXM and stimulated 17-OHP and negative correlation with DHEAS. Furthermore DXM and stimulated 17-OHP increased with AI quantity. Cortisol was rising with age and decreasing with BMI. Women presented with higher basal 17OHP than men. Mean metanephrines were higher in hypertensive subjects.
Conclusion
Even AI defined as nonfunctional show some degree of autonomous cortisol secretion. In the adrenocortical tumor tissue different steps of steroidogenesis may be altered simultanously. Intratumoral cortisol overproduction and 21-hydroxyalse deficiency might be associated with tumorigenesis especially in development of bilateral, and multiple lesions as well as tumor growth. Catecholamines production may contribute to high incidence of hypertension in AI. Ageing and body mass should be considered in interpreting hormonal abnormalities in AI patients.

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P10

Clinical, laboratory findings and results of therapy in patients with Cushing's syndrome

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Introduction
To assess the demographic data, etiological distribution, methods of diagnosis in patients with clinical (CS) and subclinical Cushing's (SCC) syndrome.
Methods
Forty-seven patients, 35 with CS and 12 with SCC patients were evaluated retrospectively.
Results
Of the 35 patients with CS, 55% were classified as ACTH-dependent and 43% as ACTH-independent. Pituitary adenoma constituted 54% of cases, adrenal adenoma 34%, adrenal carcinoma 9% and ectopic ACTH syndrome 3%. ACTH independent macronodular adrenal Hyperplasia (AIMAH) was determined in 50% of the 12 patients with SCC, adrenal adenoma in 33.3%, adrenal carcinoma in 8.3% and pituitary adenoma in 8.3%. At 1 mg DST and 2-day 2 mg DST tests used for endogenous hypercortisolism screening and diagnosis, 1.8 μg/dl cortisol threshold value sensitivities were 100 and 97.9%, respectively. When a 7.5 μg/dl threshold value was used for overnight cortisol, test sensitivity was 81.8% in clinical syndrome patients and 50% in subclinical syndrome patients. While plasma ACTH levels were above a threshold value of 15 pg/ml in all (100%) ACTH-dependent Cushing's syndrome patients, ACTH was below this threshold in all adrenal Cushing's syndrome patients. IPSS performed with CRH stimulation had 100% sensitivity and specificity in differentiating Cushing's disease from ectopic ACTH syndrome. No positive receptor response was determined in any test included in the standard screening protocol recommended for the detection of aberrant receptors in AIMAH patients.
Discussion
AIMAH was the most common cause of subclinical Cushing's syndrome in our study. Since 5–10% of incidental adrenal masses are bilateral, the number of AIMAH cases with subclinical Cushing's syndrome is expected to rise increasingly. The absence of positive response in any test in the standard protocol recommended for aberrant receptors, supports the idea that there may be other aberrant receptors. While a 1.8 μg/dl cortisol threshold value following overnight 1 mg DST and 2-day 2 mg DST had high sensitivity for detecting endogenous hypercortisolemia, a 7.5 mcg/dl threshold value for overnight serum cortisol had low sensitivity. Plasma ACTH levels above 15 pg/ml are compatible with ACTH-dependent Cushing's syndrome, while ACTH levels below 15 pg/ml are compatible with ACTH-independent Cushing's syndrome. Plasma ACTH may be between 5 and 15 pg/ml in AIMAH cases with mild hypercortisolemia and adrenal adenomas in particular. IPSS is the most reliable means for discriminating between pituitary and non-pituitary sources of ACTH.

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P11

VEGF autocrine secretion is enhanced by EGFR activation trough ERK1/2 phosphorylation in human adrenocortical carcinoma cell lines

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Adrenocortical cancer (ACC) is still orphan of medical treatment. Our preliminary data show that EGF induces ACC cell lines proliferation (+20 and +10% vs control in SW13 and NCI-H295 cell lines respectively). EGF receptor (EGFR) expression is higher and ubiquitous in SW13 cells, while it is weaker in NCI-H295 cells, where it is present only on the membrane. Aim of our study is to analyze EGFR downstream signalling in ACC cell lines.
EGF induces VEGF synthesis, therefore we investigated EGF-induced VEGF secretion in ACC cells. EGF enhanced VEGF secretion only in SW13 cells while had weak effects on NCI-H295. In addition, a VEGF receptor (VEGFR) blocking antibody significantly reduced EGF effects on SW13 cells proliferation, while it had negligible effects on NCI-H295 cells. VEGF synthesis and secretion is controlled by PKCα, PKC β2 and ERK1/2, that are involved in EGFR downstream signalling. PKCα and PKC β2 were not modulated by treatment with EGF or with Sunitinib (an EGFR inhibitor), nor by the combination of EGF and Sunitinib. ERK1/2 phosphorylation was strongly enhanced by EGF, an effect slightly counteracted by Sunitinib. These effects were more evident in SW13 as compared to NCI-H295 cells.
These data demonstrate a crosstalk between EGF and VEGF signalling pathways that is, at least in part, mediated by ERK 1/2, and could indicate novel molecular targets possibly useful in the future design of ACC medical therapy. Further studies are needed to deeply understand these pathways in ACC.

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P12

New drugs switching off Wnt/β-catenin signaling in adrenocortical tumor cells

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Introduction
Adrenocortical tumors (ACT) are common diseases mostly benign, but among them, adrenocortical carcinomas (ACC) appear highly aggressive with metastatic potential. Wnt/β-catenin pathway is frequently switched on in ACT, with β-catenin greatly dephosphorylated and consequently activated. While IWR1 induces an increase in Axin2 protein levels, XAV939 inhibits tankyrase 1 and 2 (thus stabilizing Axin): both stimulate β-catenin phosphorylation and degradation.
Aim
To investigate the role of IWR1 and XAV939 alone or in combination with mitotane in adrenocortical tumor cell lines and in primary adrenocortical tumor cells.
Methods
MTT test was performed on SW13 and H295R cells and two ACC and two cortisol producing adenomas primary cell cultures. Expression of IWR1 and XAV939 targets (Tankyrase1, Tankyrase2, Axin1 and Axin2) and β-catenin were confirmed by western blot.
Results
MTT test at 72 h revealed a concrete cell viability decrease using XAV939 (10 μM) of 52% for SW13 and 37% for H295R cells. Furthermore IWR1 at 72 h (10 μM) induced a moderate cell viability reduction for SW13 cells of 57% and for H295R cells of 30%. In SW13 cells at 72 h, combination of mitotane (10 μM) and XAV939 (10 μM) resulted in cell viability decrement of 15% if compared to XAV939 alone. No appreciably alteration was found in combination regimen for H295R cells. Furthermore XAV939 alone at 24 h was effective in 1 ACC primary cell culture, while IWR1 at 24 h showed a weak cell viability decrease in one ACC and one CPA primary cell culture.
Discussion and conclusions
Our preliminary results demonstrated the expressions of different IWR1 and XAV939 targets in adrenocortical cells. Moreover IWR1 and XAV939 seem to effectively act on Wnt/β-catenin pathway, providing evidence for their potential role on ACT treatment. Further analysis are in progress to substantiate these data.

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P13

Effects of everolimus, nilotinib, imatinib and ZOL in combination with mitotane in monolayer and spheroids human adrenocortical tumor cell line

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The primary treatment of adrenocortical carcinoma (ACC) is surgery and the adrenolytic mitotane. In order to test the effect of everolimus, nilotinib, imatinib and zoledronic Acid/ZOL in combination with mitotane were used ACC cell line NCI-H295R, in monolayer (2D) and spheroid (3D) cell cultures. The cytotoxicity promoted by treatments was analyzed by MTS and Cell Death assays. These assays were also performed intending of use them to test drugs in tumor cell cultures from patients. In monolayer, Everolimus (10 μM) reduced cell viability in 44 ± 0.10% ($P \leq 0.001$) after 72 h and apoptosis. Combination with mitotane 10 μM resulted in a significant inhibition of the cell growth, apoptosis and necrosis after 24 h (58 ± 0.13%-$P \leq 0.001$). Zol (10 μM) induced apoptosis and promoted cell viability decreased only at the maximal concentration tested (10 μM), after 72 h (28 ± 0.09%, $P \leq 0.01$). Combined with mitotane (10 μM), ZOL (5 μM) increased the cytotoxicity and promoted necrosis and apoptosis. Nilotinib decreased viability in 50 ± 0.02%($P \leq 0.001$) after 72 h, at the minimal dose tested (1 μM). However, in combination with Mitotane (10 μM) the inhibition was obtained after 24 h. Imatinib (5 μM) decreased the cell growth (18 ± 0.08%-$P \leq 0.01$) after 72 h. In 2D cell culture, Nilotinib was more potent than *Imatinib.* In contrast, the spheroids cell culture showed a lower response than monolayer, and required higher drugs concentrations. Mitotano (30 μM) and Everolimus (10 μM) suppressed cell proliferation (50 ± 0.01%, $P \leq 0.001$) after 72 h, with necrosis evidence. Mitotano30 μM and Nilotinib5 μM inhibited cell proliferation (41 ± 0.06% $P \leq 0.001$) after 24 h, and showed late apoptosis. There was no difference between the Mitotane used alone and in combination with ZOL. In summary, Nilotinib and Everolimus were more efficient in combination with Mitotane, in both 2D and 3D cell culture. There are differences in the efficacy of the drugs in the 3D cell culture, suggesting the spheroids and MTS assay as important tools for the preclinical evaluation of the cytotoxic effect of anticancer agents.

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P14

Two uncommon adrenal incidentalomas

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Incidentally discovered adrenal masses (adrenal incidentalomas) are found with increasing frequency due to the widespread use of imaging techniques of the abdomen. Most likely etiology of adrenal incidentaloma is benign non-functional adenoma. But there are rare causes like schwannoma and ganglioneuroma. During 2000 and 2013, we followed 248 adrenal incidentaloma cases that 38 of them operated. Here, we report two of them with the diagnosis of adrenal schwannoma and ganglioneuroma which thought to be rare causes.
Case 1: adrenal ganglioneuroma
A 18-year-old male with lower quadrant pain underwent an abdominal ultrasonography which revealed 5 × 7 cm left adrenal mass. A thorough investigation of this mass revealed it to be a non-functioning tumor. Magnetic resonance imaging (MRI) and ^{18}F-2-fluorodeoxy-D-glucose-positron emission tomography (PET-CT) were also performed before surgery. The final pathology report revealed a ganglioneuroma.
Case 2: adrenal schwannoma
A 32-year-old woman with bloated feeling and stomach ache was incidentally found to have a left adrenal mass of 9 cm on abdominal ultrasonography. Computed tomography (CT) of the abdomen and PET-CT were also performed before surgery. Metabolic evaluation was unremarkable. Due to the large size of

the tumor left adrenalectomy was performed. Histological examination established the diagnosis of schwannoma. This is the first schwannoma case with PET-CT imaging.
Conclusion
With increased and improved use of diagnostic imaging techniques it is predicted that the number of adrenal incidentalomas detected will continue to rise. Awareness of common and uncommon benign and malignant lesions of adrenal is vital for accurate pathological diagnosis to guide optimal patient management.

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P15

Cushing's syndrome in women with polycystic ovary syndrome

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Aim of this study was to investigate the incidence of Cushing's syndrome (CS) in women with polycystic ovary syndrome.
Materials and methods
The study involved 35 women from 17 to 39 years with verified diagnosis of PCOS according to the Rotterdam Consensus (2003). First group – 26 women with PCOS and BMI $\geq$ 25 kg/m^2 and second group – control – nine women with PCOS and BMI $\leq$ 25 – 18 kg/m^2. Investigated endocrine and gynecological status, levels of LH, FSH, DHEAS, cortisol, ACTH, testosterone, prolactin, progesterone, estradiol, performed ultrasound of the ovaries and uterus, pituitary MRI and CT adrenals. At higher levels of cortisol or ACTH determined the rhythm of cortisol secretion.
Results and discussion
In first group in 72.3% the disease began from increase in body weight, 21.3% with menstrual dysfunction (MD), 6.4% is not installed. The main complains of patients was an increase in body weight (86.2%), MD (91.2%), increased hair growth on the body (45.7%), greasiness of the skin and hair (32.6%), the appearance of stretch marks on the skin (28.6%). Objectively 23.5% of patients with established obesity, striae – 33.5%, greasiness of the skin and acne rash – in 13.5% of patients.
In second group the main complaints were MD (78.3%), hirsutism-31.7%, and infertility (10.4%). By ultrasound follicle persistence occurs in 65% of patients. Ultrasound picture of ovarian/uterine shows that in 36% increase ovarian volume, in 12% uterine hypoplasia, 32% small cystic structure, 25% polycystic structure, 43% multifollicle structure, 47% the persistence of the follicle, the follicle atresia 32%.
In first group patients in four women found increased levels of cortisol. In further examination, three of them had ACTH-dependent CS, in one case makronodular adrenal hyperplasia.
Conclusion
Patients with PCOS are at risk for the development of the CS. Frequency of CS in women with PCO 4/35, is 11.1%, much higher than expected frequency in the general population.

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P16

Adrenal hormons substitution in MElas syndrome

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Introduction
MElas syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like episodes) is a mitochondrial disease conditioned by mutations in mitochondrial DNA and inherited in the maternal line.
Case report
A boy, aged 9, with correct pregnancy II, birth weight 3450 g and of healthy, young parents was admitted to the Department of Endocrinology and Neurology, Medical University of LUblin in a severe condition, with left-sided hemiplegia and convulsions. Anticonvulsant treatment in high doses did not produce lasting effects – large collective seizures were repeating. MRI was carried out twice and stroke-like focuses were found. They were occurring alternately in both hemispheres of the brain. The focuses disappeared in shorter time than the healing ability of a typical stroke, indicating the vasomotor nature. During the treatment, the boy experienced significant weakness, muscle adynamia, electrolyte disorders: hyponatremia, hyperkaliemia, and recurrent episodes of hypoglycemia. Additional tests showed very low cortisol levels and the lack of rhythm in its secretion, ACTH levels were within the normal range. After applying high doses of Hydrocortisone in combination with antiepileptic drugs clinical improvement was achieved as well as the return of muscle strength and collective seizures disappeared. The computer tomography showed complete atrophy of the right adrenal gland. A year after the onset of the disease, both left adrenal gland involution (in the computer tomography) and deepening shortage of mineralocorticosteroids (boy requires constant treatment with mineralocorticosteroids) were observed.
The patient's brother, sister, and parents were genetically tested. MElas syndrome was confirmed in the boy's older brother. The mother and daughter are carriers of the disease. There were no genetic disorders of mitochondrial DNA in the father.
Conclusion
Symptomatic treatment, including substitution of adrenal hormones, can improve the comfort and possibly extend the lives of patients with MElas syndrome.

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P17

Female to male gender identity disorder in a patient with non-classical congenital adrenal hyperplasia

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Introduction
Congenital adrenal hyperplasia (CAH) is a prevalent disturb in female to male gender identity disorder (GID). However, psychoendocrinology of GID is not yet fully understood.
Case Report
A 22-year-old patient(46, XX), was sent from Psychiatry-Sexology to Endocrinology consultation for GID to start hormonal treatment. Self-awareness as a male began at 12-year-old. Menarche at the age of 13 years. At 14-year-old, it was noticed overgrowth of terminal hair with male pattern. Since 16-year-old with oligomenorrhea. No history of previous hormonal therapy. On physical examination, signs of virilization - hirsutism (Ferriman Gallwey scale score: 32), clitoromegaly and deep voice - and android obesity (W = 106 Kg, H = 1.80 m, BMI = 32.7 Kg/m^2). Laboratory assays showed increased 17 OH-progesterone (8.3 ng/ml (0.42–3.5)), androstenedione (9.59 ng/ml (0.6–3.1)) and ACTH (157.1 ng/l (< 13.3)) levels. Total testosterone, SHBG and DHEA-s were in the normal range for females. Pelvic ultrasound documented increased ovary size with multiple bilateral peripheral millimetric cysts. Synacthen test confirmed the diagnosis of CAH (17-OH progesterone > 10 ng/ml (30.5) 60 min after tetracosactide), excluding cortisol deficiency. Molecular study of 21-hydroxylase genes enabled the detection of a mutation c.290-13 (A / C > G) in heterozygosity, and *P*. Val281Leu in homozygosity in CYP21A2 gene, confirming the diagnosis. The patient began hormonal therapy with testosterone enanthate (250 mg IM every 4 weeks) to optimize the phenotype and achieve male physiological levels of testosterone.
Discussion and Conclusion
According to the genotype-phenotype correlations described in the 21-hydroxylase deficiency, it was expected that these combinations of mutations were associated with a non-classical variant of the disease, being unexpected this severe virilizide presentation. It can be questioned if this deficiency may have conditioned the GID and whether an earlier diagnosis and timely hormonal treatment could have influenced the disturbance.

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P18

Adrenal function in glucocorticoid-treated patients with acute exacerbations of COPD: the 'REDUCE*' randomized trial

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Introduction
Systemic glucocorticoid therapy may put patients at risk for later adrenal failure during times of stress, but tapering increases cumulative steroid exposure. We prospectively evaluated adrenal function and clinically relevant hypocortisolism after abruptly stopping prednisone treatment in patients with exacerbated COPD.
Methods
This is a pre-specified analysis of the REDUCE randomized trial (*Journal of American Medical Association*, 2013). Patients were treated with 40 mg prednisone daily for 5 or 14 days in a placebo-controlled fashion. Adrenal function was assessed by the low dose (1 μg) Synacthen stimulation tests (SST) prior to administering the first glucocorticoid dose, on day 6 before initiating blinded treatment, and on the day of discharge. The test was performed on day 30 if patients were biochemically suppressed at discharge, and repeated on days 90 and 180 unless results became normal. Patients with pathological tests at discharge were instructed about hydrocortisone substitution in situations of stress.
Results
From a total of 311 patients, 274 patients underwent SSTs and were included in this analysis (mean age 69.7 years, 61.3% males). SSTs were pathological at baseline in 15%. Mean basal/stimulated serum total cortisol levels were highest on admission (496/816 nmol/l) and lowest on day 6 (235/453 nmol/l), showing a steady increase thereafter. Among the patients tested, insufficient SST were found in 63, 38, 9, 3, and 2% at time points day 6, discharge, and days 30, 90, and 180, without significant difference in patients with 5 or 14 days exposure ($P > 0.05$). There were no hospitalizations or deaths due to adrenal crisis.
Conclusions
Despite frequent biochemical adrenal suppression, stopping systemic glucocorticoids abruptly after up to 14 days treatment with 40 mg prednisone daily appeared safe in patients provided with instruction on stress prophylaxis.

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P19

Acute pasireotide suppression test in patients with Cushing's disease: a role in predicting long-term efficacy?

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Introduction
Pasireotide is a multireceptor-targeted somatostatin analogue effective in the treatment of patients with Cushing's disease (CD) but associated with an increased risk of hyperglycaemia. We prospectively investigate the role of an acute pasireotide suppression test (PST) in predicting long-term response in CD.
Methods
Eleven patients with CD (seven females, four males; mean age 45 ± 17.3 years) received at 0900 h a single s.c. injection of 600 μg pasireotide. ACTH and cortisol levels were assessed before and every 2 h for 8 h after drug administration and then at midnight. Salivary cortisol was assessed before pasireotide administration, after 2 h and then at midnight. Blood glucose was measured before and then after 2 h after drug administration.
A partial response was defined as a reduction in hormonal parameters of 25–49% from baseline from 2 to 8 h after drug administration while a reduction $\geq 50\%$ was considered as a complete response.
After acute PST, all patients were continued on pasireotide 600 μg s.c. twice a day.
Follow-up data at month 3 are available for seven patients.
Results
A single-dose of 600 μg pasireotide decreased serum cortisol in 82% of patients (partial response in 4/11 and complete response in 5/11 patients). Regarding plasma ACTH, a partial response was achieved by 2/11 patients and a complete response by 5/11 patients. Midnight serum and salivary cortisol decreased with a restoration of cortisol rhythm in three patients. After 2 h from pasireotide administration glucose levels increased in all patients.
After 3 months, two patients with a complete response and three with a partial response to acute PST, normalized 24 h urinary free cortisol (UFC) levels. Two patients with a positive response to acute PST had decreased 24 h UFC by more than 25%.
Conclusions
A positive response to acute PST seems to be associated with a positive response in the medium-term.

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P20

Measurement of serum total cortisol using HPLC coupled ESI–TOF mass spectrometry

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Cortisol is a glucocorticoid hormone with low molecular weight (362 Da) synthesized from cholesterol in the adrenal gland. The release is regulated by the hypothalamic–pituitary-adrenal (HPA) axis. Approximately 95% of the circulating amount is bound to proteins (CBG and albumin), but only the remaining free fraction is biologically active. Serum cortisol level is routinely analysed in laboratory medicine, though the widespread immunoassays (RIA and ECLIA) have the disadvantage of cross-reactivity with some commonly used steroid drugs, which can be eliminated by mass spectrometry. On the other hand in routine diagnostics we only have the opportunity to measure total cortisol concentration, but the identification of free cortisol provides more informative results. MS has become a method of increasing importance for cortisol estimation because after suitable sample preparation it provides the measurement of free fraction as well. Our aim was to develop a mass spectrometric method to analyze serum total, serum free, and salivary cortisol based on accurate mass identification, which can be reliably used in diagnostics and in therapy follow-up. The analysis was carried out on a Bruker micrOTOF mass spectrometer using deuterated (9,12,12-D3) cortisol as internal standard. Sample preparation involved protein precipitation, serum ultrafiltration, and solid phase extraction. The limit of detection (LOD) for total cortisol measurements was 9 nmol/l and the limit of quantification (LOQ) was 15 nmol/l. The calibration curve was linear from 25 fmol to 1046 pmol (on column). Average intra-assay variation was 3.1%, while the inter-assay variation was 6.3%. Results were compared with the data of the Roche Modular Analytics E 170 ECLIA assay. The comparison resulted in eligible correlation ($R^2 = 0.96$, slope $= 0.9725$, CI 0.971–0.991 at 95%) in every (low, medium, and high) concentration range.
We can conclude that MS coupled with HPLC has higher specificity compared to immunoassays as identification is based on compound mass, instead of structural characteristics. We did not observe any interference with the therapeutically used steroid drugs, which is a common limitation of the immunoassays. Our method is capable of specific cortisol quantification in different matrices based on accurate mass identification.

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P21

Hypoaldosteronism post Conn's adenoma retroperitoneal adrenalectomy presenting with acute renal failure and hyperkalaemia requiring mineralocorticoid replacement

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A 58-year-old presented with a 19 years history of hypertension and hypokalaemia for 10 years. Her diagnostic workup confirmed autonomous hyperaldosteronism with an aldosterone of 400 pmol/l, plasma renin activity <0.2 pmol/ml per h, ratio >2000. Aldosterone failed to suppress at 430 on the saline suppression test. There was a 1.3 cm right adrenal adenoma on CT scan, Hounsfield units 21. Adrenal vein sampling showed a convincing right: left ratio aldosterone: cortisol ratio of 22 with an adequate left adrenal: IVC ratio of $<50\%$. Cortisol suppressed appropriately on the low dose dexamethasone suppression test to 30 nmol/l and urine catecholamines and metanephrines were normal.

Histology after retroperitoneal adrenalectomy confirmed an adrenal cortical adenoma. Soon after the patient was admitted to hospital complaining of palpitations with shortness of breath. CTPA was negative, ECHO showed a LV hypertrophy with a normal EF and a mild multivalve regurgitation. Twenty-four hours ECG showed occasional nocturnal bradycardia, two ventricular ectopics and occasional supraventricular ectopics.

She was then readmitted with an acute kidney injury and hyperkalaemia of 6.6 which was felt to be due to hypoaldosteronism with contralateral adrenal suppression from prolonged hyperaldosteronism. ARBs were then stopped and 300 μg fludrocortisone started.

The β blockers were switched to calcium channel blockers and her renal functions normalised. She remained hypertensive so we titrated the fludrocortisone dose down and the antihypertensives up till we optimised her BP.

This case highlights the fact that the renin–angiotensin aldosterone system feedback system is complex and could be overridden by autonomous aldosterone oversecretion that may need time to recover after the Conn's adenoma resection.

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P22

Hyponatremia as a predictor of in-hospital mortality

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Background

Hyponatremia is the most common electrolyte abnormality, it increases morbidity and mortality, but it is not clear if this condition influences mortality independently of other contributing factors. The aim of our study was to assess the relative contribution of hyponatremia to in-hospital mortality and to determine predictive factors associated with hyponatremia-related mortality.

Materials and methods

A database search was conducted for all patients admitted to Fifth Department of Internal Medicine of University Hospital in Bratislava Slovakia, from 1st January 2012 to 31st August 2012**.** Medical records were reviewed and patients demographics, underlying disease, cause of hyponatremia, and in-hospital deaths were noted. Control group consisted of patients with normonatremia admitted to the same department during the same period matched 1:1 by sex, age and underlying disease. Difference in in-hospital mortality rate between the study and control groups was tested by χ test. Baseline demographics, underlying diseases, cause of hyponatremia, and state of hyponatremia correction as possible risk factors for mortality were tested in a multivariate analysis.

Results

The baseline cohort of all admitted patients consisted of 2171 patients. Hyponatremia was found in 278 (13%) patients (160 females and 118 males). The most common causes of hyponatremia were gastrointestinal loss (52 patients), decreased oral intake (47 patients), and dilution hyponatremia (45 patients). The in-hospital mortality in hyponatremic group was significantly higher compared with control group (22 vs 7%, respectively; OR 3.75, 95% CI 2.17–6.48, $P<0.0001$). In a multivariate analysis independent factors associated with increased mortality were age above 65 years, dilution hyponatremia and decreased oral intake as etiologic factors of hyponatremia, unsuccessful hyponatremia correction.

Conclusion

Hyponatremia is an independent factor of in-hospital mortality. Age above 65 years, failure to correct hyponatremia and some specific etiologic factors of hyponatremia increase mortality.

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P23

A case of an accessory spleen mimicking a nonfunctional incidentaloma

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Introduction

The diagnosis of an increasing number of adrenal tumors, so-called 'incidentalomas', is the result of technological advances in imaging such as abdominal ultrasonography (USG), computed tomography (CT) and magnetic resonance imaging (MRI). We present a case of an accessory spleen mimicking a nonfunctional incidentaloma.

Case

An 18-year-old boy was referred for evaluating of left adrenal mass that was detected by USG performed for abdominal pain. Physical examination and laboratory findings were normal. CT showed a 22×14 mm, left, non-adenom mass at 43 Hounsfield units (HU) with an absolute wash-out value of 58%. The mass, being compatible with a non-adenoma lesion, did not show a signal lose on out-of-phase images with MRI, confirming CT findings. Evaluation for hormonal secretion did not show any hormonal excess suggesting the lesion was non-functional. As adrenal carcinoma could not be excluded by imaging laparoscopic adrenalectomy was planned. During the operation, the surgeon noticed that the adrenal gland was completely intact and the appearence of the regular shaped lesion was similar to the spleen suggesting an accessory spleen by macroscopic examination. A frozen section analysis revealed that the lesion was an accessory spleen. The lesion was completely resected, the pathologic evaluation confirmed the final diagnosis.

Discussion

Accessory spleen detected at frequencies of 10–30% may mimic pancreatic or gastrointestinal tumors, adrenal masses, and even testicular tumors. It is still controversial whether adrenalectomy should be performed or not in the case of small incidentalomas because of the low possibility of malignancy. We decided to perform surgical removal of the mass since the image findings could not rule out a malignant tumor. It is suggested that the possibility of accessory spleens when a left nonfunctional adrenal tumor is suspected by conventional imaging techniques should be born in minds.

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P24

Bone mineral density, markers of bone remodeling, and quality of life in patients with Cushing's syndrome after 12 months of remission

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This study estimates the recovery of bone mineral density (BMD), markers of bone remodeling and quality of life in patients with endogenous Cushing's syndrome (CS) after 12 months of remission.

Materials and methods

Twenty-one patients with CS were prospectively evaluated at active stage of the disease and after being in a full remission (substitutional therapy with hydrocortisone or normal 24 h urinary free cortisol (24 h UFC) and late-night cortisol) during 12 months. A thoracic and lumbar X-ray was performed to reveal vertebral fractures. BMD was measured by DXA (Lunar). Markers of bone remodeling were assayed by ECLIA Cobas e601 Roche. Patients fulfilled EQ-5D,

ECOS-16 questionnaires and performed 'up-and-go', 'tandem', and 'chair-rising' tests.
Results
Among enrolled patients 17 were females; four males; median of age (Q25–Q75) – 41 (33–49) years old; in ten cases (48%) low traumatic fractures were diagnosed. After the achieving remission no new fractures were registered and significant improvement in *Z*-score was revealed: L1–L4 −1.8 (−2.6 to −0.5) vs −1.2 (−2.2 to −0.5) ($P=0.05$); Neck *Z*-score −0.9 (−1.7 to −0.8) vs −0.7 (−1.6 to −0.3), $P=0.003$. Osteocalcin increased from 8.2 (6.9–12.0) to 22.7 (12.1–36.5) ng/ml, $P=0.01$ and carboxyterminal cross-linked telopeptide of type I collagen from 0.35 (0.22–0.63) to 0.7 (0.28–1.05) ng/ml, $P=0.01$. The quality of life significantly improved at all dimensions if measured by ECOS-16. According to the EQ-5D patients suffered less from pain 1.35 (0.49) vs 1.12 (0.34) , $P=0.04$ and reported the improvement in their health (visual analogue scale) from 49 (18.9)–68 (10.9), $P=0.004$, but did not differ in others dimensions. Although 100% of patients admitted the improvement in their functional ability, the difference in functional tests did not reach statistical significance.
Conclusions
Achieving remission of CS during 12 months improves BMD and quality of life in patients with CS. However, longer time is needed for a full recovery.

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P25

Subclinical hypercortisolemia: who should be operated?

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Objective
According to some authors a higher incidence of subclinical hypercortisolaemia is found among patients with bilateral adrenal tumors with benign phenotype than with unilateral ones. The question is whether all patients with bilateral adrenal tumors and subclinical hypercortisolemia should undergo surgery and, if yes, which of the tumors should be removed first.
Patients and methods
The investigated group consisted of 25 patients with benign bilateral adrenal tumors and subclinical hypercortisolemia. Measurements of cortisol concentration at 0800, 2200 and the following morning after dexamethasone suppression were done. Blood morning levels of ACTH, DHEAS, 17OHPG, concentration of HbA1c bin, and lipid fractions were determined. 24 patients were operated. The adrenal gland for removing was typed basing on scintigraphy or on tumor diameter. The above listed measurements were repeated 1, 6, and 12 months after surgery.
Results
In all operated patients the biochemical signs of hypercortisolaemia ceased after surgery. However only in 14 (58%) of them the clinical improvement was evident. Only subjects with deteriorated control of diabetes, hypertension or a quick increment of body mass before surgery have experienced benefits from surgical treatment.
Conclusion
Even though unilateral adrenalectomy brings about regression of subclinical hypercortisolemia in all operated patients with bilateral adrenal tumors, the clinical improvement is apparent only in cases with worsening of comorbidities (hypertension, obesity, and type 2 diabetes).

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P26

Recovery of the hypothalamo–pituitary adrenal axis following successful surgical treatment in various forms of Cushing's syndrome

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It is well known that successful treatment of Cushing's syndrome (CS) leads to transient adrenal insufficiency due to suppression of the hypothalamo–pituitary–adrenal (HPA) axis by the long-standing cortisol excess. Reports on HPA recovery in recent years including CS patients with less florid clinical features are scarce. Herein we report our findings in a series of patients with various forms of CS successfully treated in our department over the last 15 years.
We studied 59 patients with CS (11 men, 48 women, mean age 44.1 ± 1.51 years) who underwent curative surgical resection: 20 had Cushing's disease (CD), 34 adrenal adenomas (AA), and, five ectopic ACTH secretion (EAS). Cure was documented by low postoperative morning serum cortisol levels. Each patient received hydrocortisone replacement after surgery and was re-evaluated every 3–6 months with an ACTH stimulation test (250 μg Synacthen). Patients were also monitored carefully for symptoms and signs of adrenal insufficiency. Mean follow-up time from cure was 54.7 ± 9.99 months. At the latest follow-up HPA axis has recovered in 33 patients (55.9%) while in 26 was still suppressed. The former group had significantly longer follow-up period (75.4 ± 16.30 vs 28.5 ± 6.7, $P=0.0011$). The mean time of HPA axis recovery was 23.4 ± 3.2 months. At latest follow-up, HPA recovery was noted in 60% of CD, 50% of AA, and 80% of EAS patients. There was no correlation whatsoever between pretreatment morning ACTH/F/DHEAS, midnight F and UFC levels with the time-length of HPA suppression in the whole patient group, as well as in the subgroups of CD and AA patients.
In conclusion HPA axis recovery of patients with various forms of CS still requires a substantial time-length after the successful treatment of hypercortisolism. Pretreatment hormonal levels do not correlate with this time-length.

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P27

A three generation family with low cortisol, CBG deficiency, chronic fatigue and pain, lipomatosis and behavioral alterations

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Introduction
CBG is the main transport protein for glucocorticoids in blood. *CBG* gene is a member of the serine protease inhibitor family, located at chromosome 14q32. Inherited CBG deficiency (MIM 611489) is a rarely recessive disorder, and the phenotype associated includes low cortisol levels, presence of normal ACTH levels, hypotension and fatigue, although the exact pathophysiological mechanisms involved remain uncertain. We identified a family with a complex phenotype, that includes low free cortisol levels, lipomatosis, chronic fatigue, pain and CBG deficiency, with a segregation suggestive of a monogenic inheritance. Aim of the study is to explore which gene is involved in this complex disease suggestive to be hereditary.
Description of methods/design
We quantified the plasmatic concentration of CBG protein both in our family ($n=9$) than in a group of healthy controls ($n=15$) by using a commercial kit. Molecular analysis of four coding exons of *CBG* gene was performed by direct sequencing. Segregation analysis of parental alleles was performed through linkage analysis.
Results
Salivary and LC–MS/MS analysis identified very low free cortisol levels in two childrens and in the father, despite normal ACTH levels, with cortisol levels at the end of normal range in the sister and paternal grandfather. The maternal grandfather, the father and the two male children presented low plasmatic CBG levels. Paternal grandfather presented CBG levels at the end of the normal range. No mutations were identified in the *CBG* gene coding-regions. We identified only five SNPs. Linkage analysis identified a likely paternal transmission of the CBG alleles.
Conclusion
With the hypothesis that our family is affected by inherited CBG deficiency, molecular analysis of non-coding regions and functional studies of *CBG* gene will

be performed. In addition, the involvement of supplementary gene-disease will be demonstrated by cGH array and exome sequencing analysis.

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P28

Adrenal incidentaloma: current situation in Lithuania

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Adrenal incidentaloma is adrenal tumor incidentally discovered in the region of adrenals, usually investigating for non-endocrine disease.We attempted to find out the current situation of adrenal incidentaloma in Lithuania.
The object of research – patients who visited the Lithuanian University of Health Sciences, Kaunas Clinic's Clinic of Endocrinology and Vilnius Endocrinology Center for suspected adrenal pathology in 2007–2011. The total number of the cases in Kaunas was 1195. A retrospective study of 104 cases, applying a non-repayable simple random sampling was completed.
Analysis of the case histories showed that the most part of the patient, for the consultation of third level endocrinologist, were diverted by various specialists from Lithuanian University of Health Sciences, Kaunas Clinics in suspicion of adrenal incidentaloma accidentally detected during computed tomography or magnetic resonance imaging study. The other part of the patients were refered by family physicians of uncontrolled hypertension, heart disease, or suspicion of pheochromocytoma. The most common reason for consultation at the first visit in 2007 were pheochromocytoma (44%) and incidentaloma (40%), less frequently the primary diagnosis was named hyperaldosteronism (15%), and Cushing's disease (in 1% of all cases). Comparing data of 2007 and 2011, the situation has not changed. Pheochromocytoma as a primary diagnosis was indicated in 44% and incidentaloma in 42% of cases in 2011. A detailed examination of the patients showed a different distribution of the diseases. At Kaunas, out of 104 cases, 36 cases of incidentaloma, two cases of pheochomocytoma, two – aldosteroma, and six – drenal tumour associated with thyroid nodule. At Vilnius 13% had aldosteroma, 8% pheochromocytoma, and 12% adrenal hyperplasia.
From 2007 to 2011 cases of adrenal tumours increased twice. In Lithuania incidence of adrenal incidentaloma depends on the availability of visual research methods and adrenal biochemical markers. Prospective study of adrenal incidentaloma at the national level is discussed.

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P29

The treatment with glucocorticoids in congenital adrenal hyperplasia: short- and long-term effects of the switch from conventional glucocorticoids to 'dual release' hydrocortisone on metabolic and hormonal profile

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Life-long glucocorticoid (GC) treatment is needed in patients with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency in order to replace cortisol deficiency and to control ACTH and consequently androgen levels. Therefore, patients with CAH tend to have an increased risk of metabolic syndrome (MS), probably due to cortisol overexposure, caused by multiple daily doses of conventional GCs, unable to mimic cortisol circadian rhythm. The current study aimed at investigating the impact of the switch from twice or thrice daily conventional GCs to once daily dual release hydrocortisone formulation (DR-HC) on metabolic and hormonal profile in a cohort of patients with CAH. Twenty-three patients (15 F, 8 M, 19–29 years) with CAH, chronically treated with hydrocortisone (15–40 mg/day) or prednisone (6.25–12.5 mg/day) and switched to DR-HC (10–40 mg/day) entered the study. Metabolic and hormonal parameters were evaluated before and after short- (3 months) and long-term (6 months) DR-HC treatment in the entire group of 23 and in a subgroup of 15 patients, respectively. The insulin resistance was evaluated by calculating the homeostasis model assessment of the insulin resistance index (HOMA-IR) whereas the MS was estimated in line with NCEP ATP III definition. At 3-month follow-up, fasting plasma glucose ($P=0.004$) and HDL-cholesterol ($P=0.027$) levels significantly improved. At 6-month follow-up, fasting plasma glucose ($P=0.004$) significantly improved and a trend to a significant improvement was registered for fasting serum insulin ($P=0.074$). Moreover, HOMA-IR also significantly improved ($P=0.041$); a clear diagnosis of MS was performed in one patient at the baseline, but this was not confirmed after 6 months of DR-HC treatment. No significant change in morning plasma ACTH, 17-OH progesterone and androgens levels and no clinical worsening of symptoms and signs related to hyperandrogenism were observed, but a significant increase in morning serum cortisol levels was registered both after short- and long-term follow-up. In conclusion, the switch from conventional GCs to DR-HC significantly improves metabolic parameters and insulin resistance, maintaining an optimal hormone control in patients with CAH due to 21-hydroxylase deficiency.

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P30

Development of oral hydrocortisone granules with taste masking for the treatment of neonates and infants with adrenal insufficiency

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Background
Current standard treatment for adrenal insufficiency in neonates and infants is unsatisfactory as unlicensed adult dosage formulations are used. These are generally difficult to administer and may give rise to inconsistencies in dose as the content uniformity of the dosage form cannot be verified.
Methods
Infacort is a newly-developed immediate release formulation of hydrocortisone that is provided in appropriate unit dosage units (0.5, 1, 2, and 5 mg) in capsules containing multi-particulate granules. The granules are designed with a taste masking layer to permit compliant oral dosing. The objective of this study was to evaluate the pharmacokinetic performance of Infacort and its safety. Infacort exposure was compared to the adult immediate-release dosage form, hydrocortisone 10 mg tablets. This was a single centre, open-label, randomised crossover study in 16 dexamethasone suppressed healthy adults.
Results
Infacort and hydrocortisone at a dose of 10 mg are bioequivalent, as reflected by geometric LSmean 90% CI for ratios of C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ within 0.8–1.25. The majority of subjects described the Infacort as, 'not good or bad', for smell (81.3–87.5% of subjects), feel in the mouth (68.8% of subjects), and taste (68.8–81.3% of subjects).

	Infacort granules 10 mg geomean	Hydrocortisone tablets 10 mg geomean	Ratio infacort: hydrocortisone (90% CI)
C_{max} (nmol/l)	566	598	95 (84 to 107)
$AUC_{0\text{-}inf}$ (h× nmol/l)	1602	1576	101 (96 to 107)
$T_{max\ (h)}$	0.75	1.00	0.0 (−0.5 to 0.3)

Conclusions
Infacort was safe, well tolerated and of neutral taste when administered as a single oral dose of 10 mg. Infacort granules and hydrocortisone tablets were bioequivalent with respect to C_{max}, AUC, and t_{max}.

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P31

Postpartum adrenocortical deficiency: a case report

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Introduction
We report a case with primary adrenocortical deficiency after the first month of lactation.
Case report
Thirty-year-old woman was referred with complaints including dizziness, weakness and fatigue in the early *postpartum* and lactation period. On physical examination, weight 63 kg, height 164 cm, blood pressure 100/65 mmHg, pulse 96 per min were detected. She had the increase of the brown pigmentation on her hands and face. In the analyzes of the blood, fasting blood glucose 91 mg/dl (70–100), creatinine 0.8 mg/dl (0.5–1.2), potassium 4.9 mmol/l (3.5–5.5), sodium 139 mmol/l (132–146), aspartate transaminase 25 U/l (0–34), alanine transaminase 25 U/l (10-49), prolactin 123 ng/ml, LH 5.25 mIU/ml FSH 6.63 mIU/ml, estradiol 37.7 pg/ml, free T_4 0.86 ng/dl (0.54–1.24), TSH 2.89 IU/ml (0.34–5.6), cortisol 1.9 ug/dl (6-7-22,6), dehydroepiandrosterone sulfate <15 g/dl (35–430), ACTH 1453 pg/ml (7.2–63.3), the plasma renin 4.5 pg/ml (5.4–34.5), aldosterone <20 pg/ml were determined. The estimated primary adrenocortical insufficiency in patients, there was no response to the test Cosyntropin (peak cortisol levels was 2.15 μg/dl). Autoantibodies in autoimmune polyglandular involvement in terms antipariyetal antibodies were positive only. Adrenal imaging showed no pathology. Chest-X-ray and tuberculin skin test were negative. After saline infusion followed by glucocorticoid and mineralocorticoid replacement therapy, she was recovered.
Discussion
During pregnancy and *postpartum*, the prevalence of primary adrenal insufficiency is unknown. Primary adrenocortical deficiency in the postpartum periods can be diagnosed and treated, carefully.

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P32

Relative adrenal insufficiency in acute ischaemic stroke

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Introduction
Acute ischaemic stroke is a stressful condition in which there is marked increase in the production of cortisol. In the past adrenal insufficiency in critically ill patients had been shown to be associated with significant morbidity and mortality. To date there is no study performed to determine its prevalence among patients with acute ischaemic stroke.
Objectives
The aim of this study is to determine the prevalence of relative adrenal insufficiency in acute ischaemic stroke by utilizing the low dose (LD) and standard dose (SD) synacthen tests and to correlate it with inpatient hospital morbidity and mortality.
Method
Fifty-eight patients who fulfilled the diagnosis of acute ischaemic stroke within 72 h onset of a stroke were subjected to LD (1 μg) synacthen test (LDST) and 2 h later SD (250 μg) synacthen test (SDST).
Result
Based on an increment of <250 nmol/l after LDST, 38 (65.5%) patients had relative adrenal insufficiency, however using similar criteria with the SDST, only 18 (31.0%) patients had relative adrenal insufficiency. Three patients died during the study period and they had a tendency to have high baseline cortisol levels. Interestingly the non-survivors failed to mount any significant cortisol responses to both LDST and SDST. All of the non-survivors had a significant higher FBS ($P=0.006$) and poorly controlled diabetes mellitus. The diagnosis of relative adrenal insufficiency in general was not associated with any other significant clinical outcomes.
Conclusion
This is the first study demonstrating the prevalence of relative adrenal insufficiency amongst acute ischaemic stroke patients Utilizing the LDST, relative adrenal insufficiency was found in 65.5% of patients admitted with acute ischaemic stroke in which more sensitive compared to SDST. Mortality in our cohort of stroke patients was associated with failure to mount a cortisol response to both LDST and SDST.

Keywords: ischaemic stroke, synacthen test, low dose synacthen test, standard dose synacthen test, adrenal insufficiency, Scandinavian stroke score
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P33

Circadian cortisol and GH profiles in patients with Addison's disease: a comparison of continuous subcutaneous hydrocortisone infusion with conventional glucocorticoid replacement therapy

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Background
Conventional glucocorticoid replacement therapy in patients with Addison's disease (AD) is unphysiological with possible adverse effects on mortality, morbidity and quality of life. Physiological amounts of glucocorticoids are required for normal GH production and release and a chronically raised cortisol level, suppresses the secretion of GH with possible metabolic and cardiovascular consequences. The diurnal cortisol profile can likely be restored by continuous s.c. hydrocortisone infusion (CSHI). The aim of this study was to compare circadian hormone rhythms in conventional thrice-daily regimen of glucocorticoid replacement therapy (OHC) with CSHI treatment in AD patients.
Design, subjects, measurements
An open, randomized, two-period, 12-week crossover multicenter trial in Norway and Sweden. Ten AD patients were admitted for 24 h sampling of hormone profiles after 8-week of CSHI and OHC. We measured the circadian rhythm of cortisol, ACTH, GH, IGF1 and IGF binding protein-3 (IGFBP-3) in patients who underwent OHC and CSHI treatment.
Results
The mean hydrocortisone dose was 0.34 mg/kg per day (0.10) and 0.30 (0.11) mg/kg per day for CSHI and OHC treatments, respectively. CSHI provided a more physiological circadian cortisol and ACTH curves including a late night cortisol surge. The expected nocturnal augmentation of GH release more pronounced for CSHI, and IGF1 and IGFBP3 levels tended to be higher with CSHI than with OHC.
Conclusion
Replicating the circadian cortisol rhythm with CSHI treatment could have beneficial metabolic effects beyond the normalization of ACTH levels, which should lead to further research in this area. The important nocturnal GH peak was preserved in both treatment groups but more pronounced in the CSHI group. In addition, the consistently higher IGF1 and IGFBP3 levels during morning hours suggest that CSHI provides a more anabolic and physiological nighttime state.

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P34

High risk for adrenal crises in patients with autoimmune Addison's disease: health insurance data 2008–2012

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Introduction
Adrenal crisis is a potentially life-threatening complication in primary adrenal failure. Our objective was to investigate the frequency of adrenal crises in patients with autoimmune Addison's disease (AD) in the Techniker Krankenkasse (TK),

one of the largest German Health Insurance providers, that covers more than 10% of the German population.
Design
The Statutory Health Insurance (SHI) database of the TK was analysed for diagnostic codes and prescription patterns over an observation period from 01.01.2008 to 31.12.2012. After exclusion of secondary, iatrogenic or other non-idiopathic forms of adrenal insufficiency, $n=1364$ diagnoses of autoimmune mediated AD were recorded in the SHI database. A query for ICD-code E27.2 (adrenal crisis) was performed in this subgroup for the years 2008–2012.
Results
Adrenal crises in patients with autoimmune AD were documented with a frequency up to 14–17/100 patient years. While AD is more frequent in females (OR 1.6), adrenal crises occur more often in male patients (11 vs 9%). We could not find any significant seasonal or regional effects. The need for hospital admission was higher in females (10 vs 7%) and lower in patients 30–50 years of age compared to younger and older ones.
Conclusions
In this study, we indentified an unexpected and so far unknown high risk for adrenal crises in patients with autoimmune AD. Since former investigations in patients with primary and secondary adrenal insufficiency showed a distinctly lower frequency, the risk seems to be higher for patients with autoimmune induced primary adrenal insuffiency. These findings illustrate the necessity to identify the true incidence of adrenal crises and its triggering factors. If confirmed they warrant intensified efforts for the prevention of adrenal crises.

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P35

Glucocorticoid-induced adrenal insufficiency in prednisolone treated patients and how it relates to glucocorticoid dose and the duration of treatment

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Objective
We aimed to assess the prevalence of glucocorticoid-induced adrenal insufficiency in prednisolone treated patients, and its relation to glucocorticoid dose and duration of treatment.
Subjects and measures
As part of a larger study 48 patients with rheumatoid arthritis (33 women, aged 34–85 years) treated with a mean prednisolone dose of 7.0 mg (range 5–20 mg) per day, and a mean duration of treatment of 95 months (range: 6–360 months) had a 250 μg Synacthen test performed fasting, in the morning, after a mean prednisolone pause of 47 h (range: 36–60 h). P-cortisol was measured before, 30 and 60 min after Synacthen injection.
Results
Of the 48 patients 29 (60%) and 23 (48%) respectively, had an insufficient adrenal function using P-cortisol of 550 and 500 nmol/l as cut-off levels. An insufficient response was less frequently observed in patients treated with 5 mg prednisolone/day than above (33 vs 72%; $P=0.009$) with 500 nmol/l, but not with 550 nmol/l as cut-off level (50 vs 78%, $P=0.06$). P-cortisol correlated with prednisolone dose (0 min: $r=-0.36$, $P=0.01$, 30 min: $r=-0.33$, $P=0.02$, 60 min: $r=-0.34$, $P=0.02$), but not duration of treatment (0 min: $r=-0.16$, $P=0.3$, 30 min: $r=-0.06$; $P=0.7$, 60 min: $r=-0.081$, $P=0.6$).
Conclusion
Approximately half of the patients had suppressed adrenal function 47 h after the last prednisolone dose. Depending on cut-off level, an insufficient adrenal response tended to be less frequent in patients treated with 5 mg prednisolone/day, but still occurred in 33–50% of those patients. P-cortisol correlated negatively with prednisolone dose, but the correlation only explained 11–13% of the variation in P-cortisol. Duration of treatment was not predictive for adrenal suppression. The results indicate that a substantial number of patients in glucocorticoid therapy for rheumatoid arthritis need particular awareness when considering withdrawal in order to avoid life-threatening adrenal insufficiency.

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P36

An endocrine dilemma: adrenal tumor

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Introduction
While, both quality and accessibility to novel imaging technics rises, we observe a surge in detection of adrenal masses. Those tumors are accidentally found in ~ 0.4% of ultrasonographies and in 4% of computed tomography scans (CT) conducted due to other indications. In spite of high prevalence of those lesions approach to their diagnosis, follow-up and treatment is still controversial. High financial costs and possible adverse effect on health connected with their management are a matter of debate. Taking into account those arguments, we aimed at assessing the morphology and hormonal function of incidentalomas.
Patients and methods
The study was conducted on 619 patients, diagnosed in Department of Endocrinology, Metabolism and Internal Medicine in Poznań between 2004 and 2013. Group consisted of 396 women and 223 men, aged from 19 to 88 years (mean age 59.7). CT scan was performed in each case. We assed hormonal function of hypothalamus–pituitary–adrenal gland axis. Daily urine metoxycatecholamines and electrolytes excretion as well as serum aldosterone, serum renin activity and DHEA-S were measured.
Results
Hormonal activity was disclosed in 84 cases (13.6%). Among those tumors 21 (25%) secreted excessively mineralocorticoids, while 46 (54.8%) glucocorticoids. Metoxycatecholamines production was raised in 19% (16), DHEA-S in 1.2% (1). Patients with increased glucocorticoids secretion were diagnosed with: symptomatic (14) or subclinical Cushing's syndrome (32). Nodules were bilateral in 19.4% cases. We disclosed that 89.3% lesions were smaller than 4 cm, whereas only 2.7% exceeded 6 cm in maximal diameter. Hormonally active tumors were larger than inactive ones (30.9 vs 24.3. mm; $P=0.0004$).
Conclusions
Despite majority of adrenal tumors was inactive, noticeable amount posed a risk of hormonal overproduction. Cushing's and Conn's syndrome were most common diagnosis. The preponderant size of tumor was under 4 cm. Whereas activity was diagnosed more often in larger lesions, difference between the maximal diameter in hormonally active and non-secreting lesions was quite small, but significant. To sum up, every incidentaloma require comprehensive diagnostics in order to avoid the omission of hormonally active ones.

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P37

Cardiovascular outcome in patients with primary aldosteronism following adrenalectomy and mineralocorticoid antagonist treatment: prospective results of the Munich Conn Center

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The cardiovascular outcome of targeted treatment of primary aldosteronism (PA) has not been prospectively studied in large cohorts. Using the data of the prospective German Conn's registry we evaluated the effect of adrenalectomy (ADX) vs mineralocorticoid-receptor-antagonists (MRA) treatment on blood pressure (BP), serum potassium, eGFR, pro-BNP, number and WHO DDD of antihypertensive drugs. Since 2008, 181 patients have been newly diagnosed with PA and underwent subtype differentiation using adrenal vein sampling in Munich. 86 patients (53 with aldosterone producing adenoma (APA) and 33 with idiopathic adrenal hyperplasia (IAH); 36% female, median age 53 years, mean BP 153/93 mmHg, 92% hypokalemic) underwent a standardized follow-up investigation 1 year after diagnosis, and 15 patients had 3 years of follow-up. At diagnosis, 58% of patients with APA and 67% patients with IAH had resistant or WHO grade ≥ 2 hypertension. One year after intervention, mean BP fell in the APA group from 152/93 to 133/85 mmHg, with 25% patients having resistant or WHO grade ≥ 2 BP, and 19% were normotensive without medication. In the IAH group, blood pressure fell from 154/93 to 137/86 mmHg, with 42% patients

having resistant or WHO grade ≥ 2 BP. A significant lower number and DDD of antihypertensive drugs (median number in APA 1 (2) vs 3 (2) in IAH; $P<0.001$) was observed in the APA group. The decrease in eGFR was similar in both groups (-8.9 vs -4.8 ml/min per 1.73 m^2; $P=0.25$), whereas the increase in potassium was more pronounced in the APA group ($+1.0$ vs $+0.8$ mmol/l; $P<0.05$). Treatment effects were similar in patients of >60 years ($n=18$). At 3-year follow-up no differences between the two groups was seen.
These data demonstrate that MRA treatment in PA is effective with regard to BP control, but that ADX can lead to a cure of hypertension in about one fifth of the patients.

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P38

Mitochondrial thiol systems are important players in antioxidant defence for the human adrenal cortex

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Familial glucocorticoid deficiency (FGD) results from the inability of the adrenal cortex to produce cortisol in response to ACTH stimulation and can be fatal if unrecognised. The disease manifests clinically with increased ACTH and reduced cortisol levels. Our group has recently demonstrated that oxidative stress is implicated in the pathogenesis of this disorder.
We previously identified mutations in nicotinamide nucleotide transhydrogenase (NNT) in patients with FGD by targeted exome sequencing. NNT supplies the high concentrations of NADPH needed for the glutathione and thioredoxin pathways to detoxify mitochondrial H_2O_2. Recently whole exome sequencing of FGD patients with unknown aetiology identified a novel homozygous mutation in the mitochondrial selenoprotein, thioredoxin reductase 2 (TXNRD2) in a large consanguineous kindred, and two further homozygous mutations in glutathione peroxidase 1 (GPX) and peroxiredoxin 3 (PRDX3) in one individual that may act synergistically to induce oxidative damage. RT-PCR revealed that NNT, GPX1, PRDX3 and TXNRD2 are highly expressed in human adrenals and knockdown of these genes in adrenocortical cell lines causes perturbation of redox homeostasis. Oxidative stress impedes steroidogenesis but paradoxically steroidogenesis itself induces oxidative stress as a result of electron leak throughout the steroidogenic pathway. In fact the final step of cortisol production, catalysed by CYP11B1 within the mitochondria, accounts for $\sim$40% of the total electron flow from NAPDH directed at ROS production during cortisol synthesis. An efficient ROS removal network is therefore of particular importance for the adrenal cortex and may explain why FGD patients with *TXNRD2*, *NNT, GPX1* and *PRDX3* mutations present with adrenal insufficiency. Our results suggest that both glutathione and thioredoxin antioxidant systems are critical for ROS detoxification in adrenocortical cells, with their loss leading to defective oxidative stress responses, an impairment of steroidogenesis and hence adrenal insensitivity to ACTH.

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P39

Behavioural research into adrenal insufficiency (AI) patients' perceptions of AI medication, symptoms and adherence: results of a multi-country, European online survey

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Introduction
Previous qualitative studies have explored perceptions of medication among patients with adrenal insufficiency (AI) as possible determinants of treatment satisfaction. This study is the first to quantify patients' perceptions of AI medication (necessity beliefs and concerns) and their satisfaction with information and to assess whether medication beliefs and satisfaction are related to adherence.
Methods
Validated questionnaires were used to assess medication beliefs and reported adherence to medication in an online survey of AI patients recruited from the UK ($n=20$), Germany ($n=9$), France ($n=18$), Sweden ($n=12$) and Spain ($n=11$) using market research methodologies and patient support groups. Associations between medication beliefs, satisfaction with medicines information and reported adherence were examined by logistic regression analysis for causal relationships between variables.
Results
81 participants completed the survey, of which 70 met the pre-determined criteria of currently being on conventional hydrocortisone replacement therapy. Mean age was 47.4 years (range 22–73, S.D. 14.4) and 21 patients (30%) reported low adherence to medication. Although most participants were convinced of their personal need for AI medication, 26 (37.1%) expressed doubts about the need for strict adherence to dose timings, reporting sometimes/always/often taking their dose at a different time of day than advised. 45 of the 70 patients had strong concerns about their medication. Participants reported more dissatisfaction with information about potential problems than information about action/usage of their AI medication. Patients dissatisfied with information were at greater risk of low adherence. Dissatisfaction with information about potential problems of taking AI medication was associated with higher concerns $r(70)=0.375$, $P=0.001$, as was dissatisfaction with information about the action/usage of AI medication $r(70)=0.297$, $P=0.001$.
Conclusion
There were considerable unmet needs in this European sample of AI patients, including dissatisfaction with information and concerns about potential adverse effects. Patients had high necessity beliefs, but also high concerns about current medications.

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P40

21-hydroxylase autoantibody positivity is influenced by HLA genotype in South African patients with Addison's disease

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Background
Data examining HLA associations in Addison's disease (AD) from South Africa (SA) are limited. We wished to determine the HLA in South African AD patients either positive or negative for 21 hydroxylase autoantibodies (21 OH-AA) and matched healthy controls, hypothesising that certain HLA alleles could predominate, but there may be differences from Western countries.
Methods
SA patients ($n=73$) were enrolled as part of a nationwide study of AD and matched for 78 healthy control subjects' gender and ethnicity. HLA alleles were determined using DNA-based typing for DQA1, DQB1, and DRB1 class II antigens, as well as HLA-B class I antigens. Serum autoantibodies were tested at the Barbara Davis Center.
Results
There were 40 patients who were 21 OH-AA positive and 33 who were negative. In all SA-AD HLA-DR3, DR4, the combination DR3/DR4 predominated vs controls ($P\leq 0.01$). This was more pronounced in 21OH-AA+ SA-AD vs controls with nearly 65% of AD individuals having DR3 or DR4 haplotypes, vs only 38% of controls ($P=1.9\times 10^{-3}$). In addition, the DR3/4 genotype, and HLA-B8 were much more common ($P\leq 10^{-3}$ for both comparisons). DQB1*0202 was associated with protection from AD in 21 OH-AA positive patients only, but not 21 OH-AA negative patients, despite allelic similarities with high risk DQB1*0201. HLA-B8 did not have an independent effect apart from the DR3 haplotype. HLA-B7 was also higher in the 21 OH-AA+ vs 21OH-AA negative and control populations.
Conclusions
SA-AD 21OH-AA+ patients manifest with similar HLA alleles with Western countries. HLA class II haplotypes distinguish AD risk vs controls. Distinct differences in HLA were present in autoantibody positive patients, negative patients, and controls, necessitating both 21OH-AA and HLA genotype in clinical risk assessment of patients with AD. Differences in class II haplotypes are also potential contributors to the development and/or persistence of 21 OH-AA.

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P41

Periodic cushing's disease: difficult patient, difficult management

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Cyclic Cushing's syndrome is a rare, probably under-reported disorder, characterized by repeated episodes of cortisol excess interspersed by periods of normal cortisol secretion, due to both ACTH-dependent and independent causes, and should be discerned from mild or subclinical Cushing's syndrome and pseudo-Cushing's states.
We present a female patient 52 years old, with cyclic hypercortisolism clinically manifested and biologically confirmed at the age 32 (1994). After a first mild episode, next evaluation identified total remission, taking into discussion a pseudo-Cushing. A new hypercortisolism episode with response to stimulation and inhibition tests pleaded for cyclic Cushing's disease, but only in 2001 CT revealed a pituitary microadenoma. Technical difficulties made impossible the adenomectomy. In spite of the mild episodic hypercortisolism, the evolution was encumbered by complications–hypertension, diabetes, osteoporosis. Treatment with enzymatic inhibitor (ketoconazole) was started with good initial response, followed by digestive intolerance. The nodular hyperplasia of the left adrenal recommended surgical intervention (laparoscopic left adrenalectomy) with a short remission period followed by new hypercortisolism episodes, more severe and more frequent. A treatment with Dostinex induced a relative remission for a short period. Pituitary surgery and totalisation of adrenalectomy were proposed, but the patient refused. The evolutivity of the disease imposed a more targeted treatment and we included the patient into a multinational study with Pasireotide. After a short period of biological improvement of the disease, the patient presented digestive intolerance and retrieved the consent to continue the study.
Conclusions
Cyclic hypercortisolism can occur regularly or irregularly with intercyclic phases ranging from days to years and the treatment is dependent on its underlying cause. This case is important because of the prolonged evolution, and emphasize the therapeutic difficulties, since our patient had a good initial response to different classes of drugs, afterwards the patient developed resistance and/or intolerance to them.

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P42

Could DHEA-S be a novel marker at distinguishing adrenal and pituitary Cushing?

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Introduction
Endogenous Cushing's syndrome (CS) results from chronic excessive cortisol secretion. Discovering the source of disease is very important, but non-invasive tests cannot always be enough at the determination of correct location. We need more novel markers for distinguishing adrenal Cushing (AC) and pituitary Cushing (CD). We conducted this study for evaluating usefullness of preoperative DHEA-S levels at differentiating AC and CD.
Material and methods
We attended 78 endogenous CS cases who was diagnosed between 2010 and 2013 at Ankara Numune Education and Research hospital. All AC cases were at remission after surrenalectomy, and CD cases were either at remission after pituitary operation or that were indicated as CD because of IPSS results. We recorded preoperative morning ACTH,DHEA-S levels from the our hospital database.
Results
There was 58 female (%74.3), and 20 male (%25.7) cases. There was no difference at sex rates for two groups. The mean age of two groups were similar (CD 42.76 ± 12.3, AC 44.8 ± 12.1). ACTH levels were significantly higher at CD group (78.73 ± 51.7 vs 5.63 ± 5.7 pg/ml, *P*:0.00). DHEA-S levels were also significantly higher at CD group (254 ± 189.9 vs 55.86 ± 41.1 μg/dl, *P*:0.01).
We found that the level of DHEA-S 108.5 μg/dL was an apporiate cut-off point for distinguishing CD and AC. Levels above of this cut-off has reached %78.5 sensitivity and %92.3 specificity for CD.
Three cases whose ACTH level was between 5 and 20 pg/ml had DHEA-S levels below 108 μg/dl. Two of these were AC.
Conclusion
DHEA-S, is an androjen hormone which secreted from adrenal cortex by the stimulation of ACTH. Recently a publication has reported the potential of postoperative DHEA-S levels for demonstrating remission at CD. We found preoperative DHEA-S levels were significantly difference between CD and AC with a high sensitivity and specificity at the level of 108 μg/dl.

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P43

Detection of high rate of intercurrent illnesses and adrenal crisis in patients with adrenal insufficiency by using a patient's diary

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Introduction
Current understanding about the frequency of adrenal crisis in patients with adrenal insufficiency (AI) relies exclusively on retrospective data (~6.3 adrenal crisis per 100 patient-years). In addition, no data are available about the frequency of intercurrent illness events in AI patients. For the first time we prospectively used a patient's diary in recording events of adrenal crisis and intercurrent illness in AI patients.
Design
The European Adrenal Insufficiency Registry (EU-AIR) with 20 centres across Germany, the Netherlands, Sweden and the UK started enrolling patients with AI in August 2012. At enrolment, comprehensive demographic and baseline data, etiology of AI, and details of glucocorticoid replacement therapy, are collected electronically. Safety data (intercurrent illnesses and adrenal crisis) and treatment information are collected prospectively at subsequent clinic visits. Patient diaries are used to record intercurrent illnesses and illness-related dose changes between visits and are entered in the database at subsequent clinic visits.
Results
Up to December 2013, 683 patients were registered in EU-AIR (241 primary AI, 399 secondary AI and 43 CAH) resulting in a total of 165 patient years (78 py in primary AI, 74 py in secondary AI and 13 py in CAH). Diary entries revealed a mean of 2.23 events of intercurrent illness/py with no specific differences among different AI etiologies. Adrenal crisis occurred with a frequency of 9.7/100 py, ranging from 8.1/100 py in patients with secondary AI to 12.8/100 py in patients with primary AI.
Conclusions
Using a patient's diary improves the detection of intercurrent illness and adrenal crisis events in AI patients. Using this prospective methodology the rate of adrenal crisis appears significantly higher than previously suggested.

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P44

Bone mineral density does not decrease in patients with adrenal insufficiency on a low daily glucocorticoid dose over a 2 year period

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Introduction
Patients with primary adrenal insufficiency (PAI) and patients with congenital adrenal hyperplasia (CAH) receive glucocorticoid replacement therapy, which might cause osteoporosis.
Objective
i) Is bone mineral density (BMD) depending on the height of the daily glucocorticoid dose? ii) Is BMD decreasing over a 2-year period of glucocorticoid replacement therapy?
Methods
Prospective, longitudinal study including 56 patients with PAI (41 women) and 32 patients with CAH (21 women). BMD was measured by DXA scan.

Results
Patients with PAI (age 53.3 ± 14.2 years) showed no changes in BMI (26.2 ± 4.2 vs 26.3 ± 4.3 kg/m^2) or daily glucocorticoid dose per body surface (13.9 ± 3.9 vs 13.8 ± 4.6 mg/m^2) after 28.7 ± 5.8 months. No significant changes in BMD *Z*-scores of lumbar or femoral regions were detected during the study period. However, daily glucocorticoid dose per body surface significantly negatively correlated with *Z*-scores of femoral neck ($R = -0.317$, $P = 0.021$), Ward's triangle ($R = -0.333$, $P = 0.015$), greater trochanter ($R = -0.390$, $P = 0.004$), and total hip ($R = -0.340$, $P = 0.014$), but not with lumbar regions.
Patients with CAH (age 39.5 ± 11.6y) showed no changes in BMI (26.5 ± 5.3 vs 26.7 ± 5.3 kg/m^2) after 28.6 ± 5.0 months, but the daily glucocorticoid dose per body surface decreased significantly (16.2 ± 7.7 vs 13.4 ± 6.8 mg/m^2, $P = 0.036$). Despite glucocorticoid dose reduction BMD *Z*-scores of lumbar or femoral regions did not change significantly. In CAH patients no correlation was seen between BMD and daily glucocorticoid dose per body surface.
Conclusions
Adult PAI and CAH patients on low glucocorticoid doses showed normal BMD within the normal reference range, which did not change significantly after 2 years. BMD of the femoral region significantly negatively correlated with daily glucocorticoid dose per body surface in PAI, but not in CAH patients.

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P45

Markedly elevated glucocorticoids and their metabolites in an unusual case of Cushing's syndrome secondary to ectopic ACTH production from a thymic carcinoid

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A 51-year-old obese lady was admitted with multiple cerebral, pulmonary and intra-abdominal abscesses. She was referred to the endocrine team because of newly-diagnosed type 2 diabetes mellitus. The combination of apparent immunosuppression, obesity, diabetes mellitus, hypertension, hypokalaemia, osteoporotic fractures and bilateral shoulder avascular necrosis (BSAN) led to a clinical diagnosis of Cushing's syndrome (CS); this was biochemically confirmed as follows: non-suppressed overnight dexamethasone suppression test, midnight serum cortisol 4275 nmol/l (60–250), raised salivary cortisol 716 nmol/l (5–46) and ACTH 639 ng/l (0–46). Urinary free cortisol (UFC) was elevated in excess of 75 000 nmol/l (<165). Urinary steroids metabolites were markedly increased: tetrahydrocortisol 219 024 μg/24 h and tetrahydrocortisone 88 848 μg/24 h. Pituitary MRI was unremarkable. Whole body CT scanning showed a thymic tumour and bilateral adrenal hyperplasia. Octreotide scanning showed increased focal activity in the thymus. Urinary 5HIAA was only marginally raised at 55 μmol/24 h (<45 μmol/24 h) and chromogranin A was normal: 52 pmol/l (<60 pmol/l).
Infections followed a protracted course, despite treatment with antibiotics and antifungal agents. She received metyrapone prior to a thymectomy. Histology confirmed a 'paraganglioid' variant of a thymic carcinoid tumour. Post-operatively she displayed remarkable clinical and biochemical recovery, but poorly controlled diabetes, hypertension, obesity and BSAN continued to be active problems.
We describe a case of ACTH-secreting thymic carcinoid that presented with florid clinical features of CS, but no carcinoid syndrome. Profoundly elevated cortisol concentrations were observed in saliva, serum and urine (all measured using LC–MS/MS), with loss of diurnal variation. Indeed, UFC is the highest that has ever been described for ectopic CS. Contrary to conventional investigation algorithms, IPSS was not necessary to confirm the diagnosis; instead, the combination of markedly elevated ACTH, cortisol, cortisol metabolites coupled with a negative MR pituitary and a positive CT thorax and octreotide scan were sufficient to make an accurate diagnosis.

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P46

Diagnostic performance of late-night salivary cortisol measured by automated chemiluminescenze immunoassay

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Context
Late-night salivary cortisol (LNSC) measurement has been promoted as an ideal screening test for the diagnosis of Cushing's syndrome (CS). However, its performance using commercially available assays has not been widely evaluated and limited data are available on its use in population with chronic medical conditions.
Aim
To compare the diagnostic performance of LNSC (routine use) in patients with CS and in a patients's group with different medical conditions.
Methods
We studied 281 subjects: 117 normal weight healthy volunteers (HV), 47 patients with active CS, 27 patients with uncontrolled diabetes, 61 obese subjects and 29 adrenal incidentaloma. Subjects provided to bedtime saliva samples collected (2300 h) for cortisol measurements by commercially chemiluminescence immunoassay (CLIA, Access Beckman Coulter) and in subjects with abnormal value in CLIA salivary cortisol was measured also by liquid chromatography mass spectrometry (LCMS–MS).
Results
The LNSC concentrations were significantly higher ($P < 0.001$) in CS (1.61 ± 0.83 μ/dl; range: 0.63–4.33) compared with healthy subjects (0.27 ± 0.4 μ/dl; range: 0.018–0.62). The optimal LNSC cut-off value derived from ROC analysis for the differentiation between patients with and without CS was achieved at the level of 0.58 μ/dl (Cushing vs HV; SE 96.7%, SP 96.9%). However, this cut-off showed a lack of specificity when used in obese subjects (SP), and in diabetic patients (SP). Using LCMS-MS, the diagnostic performance in obese and diabetic subjects was increase.
Conclusions
This study confirms the utility of CSN in CS screening, even using a routinary method as CLIA. However, the study underlines the necessity for every single laboratory to revaluate the cut-off, especially in those conditions that can produce an activation of the hypothalamic–pituitary–adrenal axis.

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P47

Might cortisol modulate food choices in subclinical autonomous glucocorticoids hypersecretion?

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Introduction
The relationship between food intake and hypothalamic–pituitary–adrenal (HPA) axis has been studied in the development of visceral adiposity and obesity. The HPA axis may interact with the reward system, thus influencing food choices. On the other hand, it has been shown that macronutrients differently modulate the HPA axis activity.
The aim of this study was to evaluate the dietary habits in subjects with adrenal masses (adenoma or hyperplasia) with different pattern of cortisol secretion.
Materials and methods
We enrolled 36 women with adrenal masses, divided in not-secreting (NS; $n = 19$) and subclinical autonomous glucocorticoids hypersecretion (SAGH; $n = 17$) group, according to cortisol value after 1 mg-dexamethasone suppression test (NS: cortisol <50 nmol/l; SAGH: cortisol ≥50 nmol/l). Each subject underwent dietary interview and weekly food frequency questionnaire (FFQ).
Results
The two groups were not significantly different neither in anthropometric nor in metabolic parameters. Daily caloric intake was similar between the two groups as well as the percentage of macronutrients. In all subjects, post-dexamethasone cortisol values were negatively and significantly related to lipid intake ($R = -0.415$; $P < 0.05$) and positively and significantly related to glucid intake ($R = 0.400$; $P < 0.05$). The FFQ showed a significantly lower frequency of sweet foods (chocolate, candies, etc.) consumption in SAGH then NS ($P < 0.05$).
Conclusions
These preliminary data showed, for the first time, a possible relation between cortisol suppression degree and lipidic and glucidic intake in a selected cohort of

subjects. The FFQ, expression of food choice, will be completed by analyzing the size of foods. Furthermore, these data need to be evaluated in a larger cohort of subjects with SAGH.

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P48

Retrospective analysis of adrenal ıncidentalomas: a single center experience

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Background and aim
Incidentally discovered adrenal masses (adrenal incidentalomas (AI)), generally 1 cm or more in diameter, are mostly benign and asymptomatic and are often considered as nonfunctional tumors. The aim of this study was to perform the imaging characteristics, endocrinologic screening and histologic diagnoses of adrenal incidentaloma cases encountered in our institute.
Methods
This retrospective evaluation of patients with AI includes 543 cases between 2001 and 2013. Patients were 228 males and 315 females, aged between 18 and 105 years (median, 57 years).
Results
Mass size (computed tomography measurement) ranged from 5 to 150 mm (median, 21 mm). Hormonal work-up demonstrated that 76.2% of the masses were nonsecretory, 11.4% were pheochromocytoma, 9.9% were defined as subclinical Cushing's syndrome (SCS), 1.6% Cushing's syndrome, 0.5% were hyperaldosteronism and 0.5% patient concomitant secretion of glucocorticoid, mineralocorticoid, androgen, and catecholamines. Adrenalectomy was performed in 108 patients with removal of 28 adrenocortical adenomas (26%), 15 pheochromocytoma (14%), 14 adrenocortical carcinomas (13%) and other less frequent tumor types. In patients with SCS; the rate of abnormalities was as follows: cortisol nonsuppressibility after 1 mg dexamethasone in 100%, above normal urinary free cortisol in 36.4%, and low ACTH in 28.6%. No significant difference was observed in the ages among patients with adrenocortical carcinoma and adrenocortical adenomas (48.7 ± 10.7; vs 55.6 ± 11.6 years; $P = 0.066$). Patients with adenomas were significantly smaller than carcinomas (32 ± 10 vs 54 ± 35; $P = 0.037$). The survival of patients with AI that were functional evaluated was higher than those that were not (respectively; median 149, 53 months).
Conclusion
Based on these findings, an optimal diagnostic approach to an adrenal incidentaloma would consider the results of the initial biochemical and radiographic evaluations. Endocrine evaluation should be performed in all patients to identify silent states of hormone excess.

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P49

The influence of diagnostic criteria on the interpretation of adrenal venous sampling

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Objective
Recent guidelines promote adrenal venous sampling (AVS) as the reference test to document lateralised aldosterone hypersecretion in primary aldosteronism (PA). However, there are wide discrepancies between institutions in the criteria used. Our objective was to evaluate their consequences on the interpretation of AVS results.
Design and methods
All 506 AVS performed from 01/2001 to 03/2009 in our institution were included. Results were interpreted using the criteria reported in papers from four experienced institutions where Cosyntropin is not infused during AVS (Brisbane, Padua, Paris, and Turin). AVS were classified as: i) unsuccessful if they did not meet the criterion of selectivity; ii) left or iii) right if successful and meeting the lateralisation criterion on the considered side; iv) bilateral otherwise. When multiple samples were available from at least one side, we compared the classification induced by the two most extreme lateralisation ratios from all possible combinations of right and left selective samples.
Results
The proportion of AVS classified as unsuccessful was almost five times higher with the strictest criteria than with the least strict (18 vs 4%). The proportion of AVS classified as lateralised was more than twice higher with the least stringent criteria than with the most stringent (60 vs 26%).
Multiple samples where available from at least one side in 147 AVS. Patients with more than one selective sample were classified differently with the two most extreme samples combinations in 16% (Brisbane) to 18% (Padua) of cases (Fisher's $P = 0.75$).
Conclusion
Different sets of criteria currently used in experienced institutions translate into extremely heterogeneous classifications, and hence surgical decisions, for PA patients. AVS cannot be regarded as a gold standard until the most appropriate procedure and diagnostic criteria have been defined. Large and well-designed studies, preferably multicentre, are needed to resolve this issue.

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P50

The pathophysiology of aldosterone-producing adenomas associated with their tumor size: the smaller, the higher expression of CYP11B2

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The pathophysiology of aldosterone-producing adenomas (APA), especially those manifesting clinically overt hyperaldosteronism despite their small size, remains unknown. Therefore, we examined the correlation between tumor size and the status of intratumoral steroidogenic enzymes involved in aldosterone biosynthesis using immunohistochemistry. Forty patients with surgically proven APAs following adrenal venous sampling were retrospectively studied. The tumor area at the maximum diameter of the sections was precisely measured by Image J software. The status of steroidogenic enzymes was immunohistochemically analyzed according to the *H*-score system, based on both the number of immunopositive cells and relative immunointensity. Adrenal masses were not detected by computed tomography (CT) in 20 patients. Maximum tumor area obtained in the specimens was significantly correlated with preoperative plasma aldosterone concentration, urinary aldosterone excretion, the *H*-score of CYP11B1, and was inversely correlated with the *H*-score of CYP11B2. These results demonstrated that small adenomas could produce sufficient aldosterone to cause clinically overt primary aldosteronism because of the significantly higher CYP11B2 expression per tumor area.

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P51

The adrenal venous sampling is a difficult test in the localization of the primary hyperaldosteronism

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Introduction and objectives
The localization of primary hyperaldosteronism is often difficult. The coexistence of nonfunctioning adenomas is common in patients older 40 years old and small

adenomas undetectable by CT could confuse with bilateral hyperplasia. The AVS is considered the 'gold standard' test for the location of numerous guides. We describe our experience in a clinical case of primary aldosteronism.
Clinical case
We present a 58 years old woman with refractory hypertension with quadruple therapy. Biochemical analysis showed a hypokalemic alkalosis and a hyporeninemic aldosteronism (aldosterone/plasma renin activity: 130). We discard renal artery stenosis by doppler ultrasound. CT shown a 16 mm nodule with low density and homogeneous in right adrenal, and other 23 mm nodule with high density and heterogeneous in the left adrenal. The patient was diagnosed of primary aldosteronism. We tried to locate the adrenal responsible with AVS by the following protocol. We suspended antihypertensive drugs with interference in angiotensin/aldosterone axis. We administered 250 μg of ACTH i.v. 15 min before to stimulation. By sequential catheterization right femoral vein access we had baseline samples, at 30′ and 45′ in left adrenal vein, right adrenal vein, and inferior cava vein. We considered a conscious aldosterone/cortisol (A/C) >4 between both adrenal veins as confirmation of lateralization. During the performance at 30 min was impossible to catheterize the right adrenal vein for collapse, so we end the test at this time. However, we get a baseline ratio A/C adrenal left: A/C right adrenal (basal) of 18.47 (>4) which confirms a left lateralization. No major complications, except controlled pain in inguinal region were observed. Finally the patient was operated by left adrenalectomy and the arterial pressure values were normalized without any treatment.
Conclusions
The AVS is considered the 'gold standard' test for localization of adrenal adenomas. However is a invasive test, complex,with complications, and requires a trained team. Furthermore there isn't consensus in the test protocol and their interpretation. All this hinders their realization, however help to identify lateralization hyperaldosteronism, avoiding misdiagnosis, as in this case.

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P52

Late-night salivary cortisol as an initial test for Cushing's syndrome in the group of patients with obesity and type 2 diabetes mellitus

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Background
Endogenous Cushing's syndrome (CS) comprises the symptoms and signs associated with prolonged exposition to inappropriately high levels of glucocorticoids produced by adrenal cortex. Epidemiological studies reported an incidence of 0.7–2.4 cases per 1 million inhabitants per year. Late-night salivary cortisol (LNSC) is one of three currently recommended initial screening tests for CS. The advantages of LNSC are nonivasive specimen collection and minimal influence of preanalytical phase of laboratory process. Results strongly correlate with free fraction of plasma cortisol.
Aims
To screen patients with obesity and/or type 2 diabetes mellitus for the presence of endogenous glucocorticoid hypersecretion by using LNSC test. To asses LNSC value with optimal sensitivity/specificity ratio for CS diagnosis.
Subjects and methods
281 patients with obesity ($n=131$) and/or type 2 diabetes mellitus ($n=150$) were investigated. LNSC was measured by ECLIA (Cortisol Elecsys, Roche Diagnostics GmbH). Every patient with LNSC value more than 4.3 nmol/l underwent estimation of urinary free cortisol (two samples), 1 mg overnight dexamethasone supression test (DST), eventually 2 mg/8 mg DST.
Results
Median of LNSC in group of patients without CS was 7.2 nmol/l (95% CI: 6.8–7.5 nmol/l). Autonomous cortisol secretion was found in five patients, in all of them with ACTH-independent form of CS. Values of LNSC in positive subjects were 12.8, 13.4, 11.9, 32.5 respectively 23.3 nmol/l. Calculated from ROC curve, LNSC value of 11.8 nmol/l had optimal sensitivity/specificity ratio (100% sensitivity and 95.6% sensitivity) for diagnosis of CS.
Conclusions
With regard to noninvasive collection and accesibility, LNSC is adequate test for screening of patients with signs and symptoms of endogenous hypercortisolism.

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P53

Clinical characteristics and follow-up of patients with adrenal incidentalomas

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Background
The adrenal incidentalomas (AI), adrenal masses ≥ 10 mm in diameter incidentally detected, have increased their prevalence due to technological advances in imaging. The adrenalectomy is indicated in functioning adrenal tumors and in cases suspected of malignancy.
Objectives
To analyze the characteristics of patients with AI and to evaluate the clinical outcome, in terms of evolution toward hypersecretion and significant growth, during follow-up over 5 years.
Methods
Observational, descriptive and retrospective study of patients with AI observed in our Department between January and October 2013.
Results
Among the 64 included patients, 57.8% were female and the mean age of diagnosis was 58.6 ± 11.8 years. The median diameter of AI was 25 mm (range 10–85 mm). The most of AI (76.6%) had a diameter ≤ 30 mm and six AI had a diameter ≥ 40 mm. Of these six, two showed imaging features of adrenal myelolipomas (40–50 mm) and of the remaining four (diameter >50 mm) three were pheochromocytomas and the last one was a probable metastatic disease. The functionality evaluation revealed that 50 (78.1%) patients had non-functional masses, the subclinical Cushing's syndrome (SCS) was diagnosed in three (4.7%), pheochromocytoma in another three, and primary hyperaldosteronism in one case (1.6%). The median time of follow-up was 19 months, range 4–109 months. After 3 years of follow-up, one patient had a significant growth of AI (10 mm) and two acquired autonomous cortisol secretion (SCS). Eight patients (12.5%) were oriented to surgical treatment, namely due to functionality ($n=5$), structural changes ($n=2$) and significant growth ($n=1$).
Conclusion
Excluding myelolipomas, the AI ≥ 4 cm in diameter corresponded to hormonally active or malignant lesions, so adrenalectomy in these tumors seems undeniable. The percentage of AI which grew significantly and became active was low, therefore it's surely questionable the relevance of the long term follow-up of these patients.

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P54

Effects of non-physiological concentrations of glucocorticoids on apoptotic cell death of human early hematopoietic stem/progenitor cells: *in vitro* studies

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Objectives
Glucocorticoids (GCs) intervene in different physiological activities in almost all systems of the human organism. However, GCs are also potent inducers of apoptosis in many cell types and tissues. It is known, that glucocorticoid-induced apoptosis affects the musculoskeletal system, circulatory system, nervous system, endocrine system, reproductive system, and the immune system. Nevertheless, the exact mechanisms of GCs action in human normal hematopoiesis are still not clear. Besides, direct effects of GCs on hematopoietic stem and progenitor cells (HSPCs) may be obscured in the intact human organism. For this reason, the effects of GCs on hematopoietic system were analyzed in studies performed *in vitro*, and we used primary human CD34+ HSPCs as a model system.
Materials and methods
Human cord blood-derived CD34+-enriched hematopoietic progenitor cells were examined for expression of different glucocorticoid receptors (GR-α and GR-β) at the protein level by immunocytofluorescence. In addition, the GR

activity status was analyzed by detection of phosphorylated form of GR-α, the most biologically active form of GRs. Furthermore, quantitative studies of GC-dependent biological stimulation of CD34+ HSPCs were performed, and the apoptosis activity was estimated by qRT-PCR analysis of selected apoptotic genes expression, including BAX, BCL-2 and BCL-xL.
Results
It was found that GRs expression, in the total and phosphorylated forms, were detected at the protein level in the population of human early HSPCs. Moreover, exposure of human CD34+ HSPCs to non-physiological concentrations of GCs (0, 10−5, 10−4 M/l of hydrocortisone) significantly induced apoptosis in those cells, and resulted in the increased expression of mRNA for apoptosis-related BAX gene and anti-apoptotic BCL-2 and BCL-xL, when compared to established physiological dose of GC (10−6 M/l). Importantly, we observed that higher GCs doses considerably increased BAX: BCL-2 ratio.
Conclusions
This study importantly augments the current knowledge about the role of glucocorticoids in normal human hematopoiesis. Our data may provide basis for creating novel therapeutic strategies for hematologic complications in endocrine diseases.

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P55

Effects of adrenal insufficiency on body composition and metabolic indices: data from the European Adrenal Insufficiency Registry (EU-AIR)

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Introduction
Data concerning patients with adrenal insufficiency (AI) have been limited by small numbers of patients reflecting the relatively low prevalence of this disease. The European Adrenal Insufficiency Registry (EU-AIR) is a multicenter observational study of patients with both primary and secondary AI. Enrollment commenced August 2012. Comprehensive demographic data, aetiology of AI, and details of glucocorticoid replacement therapy are collected at baseline. Safety data and treatment information are collected prospectively at subsequent clinic visits. Patient diaries are used to record intercurrent illnesses and illness-related dose changes between visits. Here we present the baseline data of enrolled patients up to December 2013.
Results
671 patients were registered in EU-AIR at time of analysis (239 primary AI, 389 secondary AI and 43 CAH). Patients were of mean age 52.6±16.9 years, 55.9% female's. There was no difference in age between primary or secondary AI patients, however, the primary AI cohort showed a greater proportion of females (70 vs 48%). Mean daily hydrocortisone dose equivalents were 13.0±5.5 and 9.9±3.3 mg/m^2 BSA for primary and secondary AI respectively. BMI of primary AI males and females was 26.4±4.6 and 26.1±5.0 kg/m^2, and for secondary AI 29.3±5.0 and 29.1±6.9 kg/m^2 respectively. Waist circumference of primary AI males and females was 93.7±18.3 and 88.3±14.5 cm, and for secondary AI 102.5±12.5 and 93.1±14.9 cm respectively.
Of the overall cohort maintained on conventional glucocorticoid replacement baseline metabolic indices showed: total cholesterol 5.5±1.3 mmol/l; LDL-C 3.4±2.6 mmol/l; HDL-C 1.6±0.6 mmol/l; ApoB/ApoA1 0.657±0.267; HbA1c 5.8±1.7%; and fasting glucose 6.1±9.9 mmol/l.
Conclusions
Prospective observational data of a large cohort of patients with AI is likely to impart significant revelations regarding the impact of this disease on individuals, long-term outcomes, subgroups of patients at particular risk, and potentially allow comparison of alternate glucocorticoid regimens.

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Takotsubo cardiomyopapthy and panhypopituitarism: case report

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Introduction
Takotsubo cardiomyopathy or stress-induced cardiomyopathy (SICM) is a rare condition. Even more rare cases associated with glucocorticoid deficiency have been described.
Case report
AAGM, a 74-year-old man was admitted to the inpatient Endocrine Department because of suspected panhypopituitarism. Six months before the diagnosis of SICM was established after an acute coronary syndrome episode with no lesions found in coronary angiography and after exclusion of variant angina. In the last year, fatigue, asthenia, adynamia, loss of muscular strength, decreased libido and loss of male hair pattern distribution were noted by the patient; however several hypertensive episodes were reported; these episodes had no triggering factor, had short duration (20–30 min) and spontaneous resolution. No concomitant headaches, visual impairment, palpitation, anxiety, pallor or sweating were noticed. Blood pressure was 100/60 mmHg on physical examination that also revealed yellowish skin color. Analytical evaluation diagnosed panhypopituitarism: TSH: 4.1 (Reference value (RV): 0.35–5.5 uU/ml); FT4: 0.5 (RV: 0.8–2 ng/dl); FSH: 2 (RV: 1.4–18.1 U/l); LH: 0.2 (RV: 1.5–9.3 U/l); TT: 14 (RV: 240–820 ng/dl); ACTH: 33 (RV: 0–46 pg/ml); cortisol: 2 (RV: 4.3–23 μg/dl); GH: 0.1 (RV < 3 ng/ml); IGF-1: 32 (RV: 87–238 ng/ml). Combined pituitary testing confirmed this diagnosis. Pheochromocytoma/paragnaglioma was excluded by urinary metanephrines and normetanephrines measurement. Sellar CT scan was negative for any lesion.
Discussion and conclusion
Although SICM is a rare condition, toxicity of increased catecholamines to myocardium is well established. Few reports in the literature associate panhypopituitarism to SICM. More specifically, adrenal failure may be the link between these two identities, since glucocorticoids seem to protect myocardium against toxic catecholamine surge by maintaining membrane calcium transport function in the cardiac sarcoplasmic reticulum and maintaining phosphorylase activity and glyconeogenolysis in animal models, and therefore affecting myocardial contractility. It is tempting to speculate that panhpopituitarism may lead to compensatory hyperactivity of the sympathetic nervous system.

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Adrenal Medulla

P57

ACTH-producing pheochromocytoma presenting with Cushing's syndrome and complicated by invasive aspergillosis: a case report

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Introduction
ACTH-producing pheochromocytoma has been rarely reported, ranging from 3 to 25% of the ectopic ACTH syndrome. Moreover, a few cases of Cushing's syndrome (CS) accompanied with opportunistic infections have been reported. We experienced a case of pheochromocytoma with ectopic CS, complicated by invasive aspergillosis.
Case report
A 35-year-old woman visited our hospital because of headache for 2 months. She presented with typical cushingoid features including centripetal obesity, buffalo hump, moon face, and hirsutism. Basal plasma cortisol and ACTH, and 24 h-urine free cortisol levels were significantly high while urinary metanephrine and catecholamine levels (24 h) were slightly elevated. The endogeneous cortisol secretion was not suppressed by both low and high dose dexamethasone. On abdominal computed tomography (CT), about 2.5 cm sized heterogeneous enhancing mass on the left adrenal gland was found. There was no definitive mass lesion on sellar magnetic resonance imaging. On PET-CT, a hypermetabolic nodule was found in left upper lung. So, we performed percutaneous needle biopsy, which was revealed inflammation, not malignancy. Thereafter, we performed left adrenalectomy, and it's pathologic finding was a pheochromocytoma with positive immunohistostaining for ACTH. After surgery, biochemistry was normalized but the clinical course was fatal despite of intensive care because of invasive aspergillosis included lung, retina, and CNS.

Conclusions
If the patient who has adrenal mass showed both catecholamine and corticosteroid excess, 'ACTH-producing pheochromocytoma' should be considered as one of differential diagnosis. Meanwhile, high cortisol level is generally observed in patients with ectopic ACTH CS, it may result in fatal outcomes because susceptible to opportunistic infections. Thus, careful attention and prompt management are needed to treat these patients.

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P58

Pheochromocytomas and paragangliomas: association between tumor size and measurements of metanephrines and catecholamines

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Introduction
Pheochromocytomas (PHEO) and paragangliomas (PGL) are rare catecholamine-secreting tumors. Some authors proposed that there is a positive linear relationship between tumor size and measurements of metanephrines and an absence of association with catecholamine levels.
Objectives
To review and characterize patients diagnosed with PHEO and PGL in Garcia de Orta Hospital. To determine the relationship between tumor size and measurements of urinary total metanephrines and total catecholamines.
Methods
Retrospective study with revision of medical records, between 1992 and 2013. Statistical analysis was performed by simple linear regression using SPSS 20.
Results
Twenty-three patients diagnosed with PHEO and PGL were identified, corresponding to 13 men (56.5%) and ten women (43.5%). Eighteen cases (78.3%) presented with unilateral PHEO, three cases (13%) with bilateral PHEO and two cases (8.7%) with PGL. We found the following genetic syndromes: multiple endocrine neoplasia type 2A (three patients), neurofibromatosis type 1 (two patients) and familial PGL type 4 (one patient). After surgery local recurrence occurred in two cases. Metastasis was identified in three other individuals who had persistence of disease despite additional therapy. We noticed a strong positive linear relationship between tumor size and measurements of urinary total metanephrines ($r=0.72$, $P=0.004$). A linear association between size and levels of urinary total catecholamines was not identified ($r=0.5$, $P=0.171$).
Conclusion
This study suggests that an increase in the size of PHEO and PGL is related with a rise in metanephrine levels; an association with catecholamines was not demonstrated. These differences may be related to the fact that the secretion of catecholamines is intermittent, whereas metanephrine formation is a more continuous process.

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The value of metanephrines and normetanephrines influences blood pressure in patients with pheochromocytoma?

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Catecholamines can cause hypertension by increasing heart rate and cardiac output or by peripheral vasoconstriction.
Aim of study
The value of plasma and urinary metanephrines and normetanephrines does not correlate with blood pressure in pheochromocytomas.
Material and methods
The lot of study consist of 35 patients with isolated pheochromocytomas diagnosed between 1985 and 2005 in National Institute of Endocrinology C.I.Parhon Bucharest. All patients had high levels of plasma and urinary metanephrines and normetanephrines and the diagnosis has been confirmed by imaging and the pathological examination.
Results
29 patients (82.9%) had high blood pressure and six patients (17.1%) had normal value of blood pressure. The mean value of plasma metanephrines and normetanephrines was 445.828 ± 127.092 pg/ml respectively 684.966 ± 91.932 pg/ml for patients with high blood pressure and 436.167 ± 107.121 pg/ml respectively 632.000 ± 65.422 pg/ml for patients with normal blood pressure. The mean value of urinary metanephrines and normetanephrines was 1011.690 ± 190.145 μg/24 h respectively 795.000 ± 72.872 μg/24 h for patients with high blood pressure and 930.833 ± 147.391 μg/24 h respectively 768.333 ± 89.536 μg/24 h for patients with normal blood pressure. Althought the mean plasma and urinary metanephrines and normetanephrines values were higher in patients with pheochromocytomas these differences are not statistically significant ($P > 0.05$).
Discussion
There are patients with pheocromocytomas and normal blood pressure althought they have high plasma and urinary metanephrines and normetanephrines. This can be caused by the adrenergic desensitization, can occur in homozygous patients for polymorphism of β2 adrenergic receptors or can be due to various reflex mechanism.
Conclusions
In our lot of study the value of plasma and urinary metanephrines and normetanephrines has not correlated with blood pressure althought their value was higher in patients with hypertension.

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P60

Olygosimptomatic malignant pheochromocytoma treated with ^{131}I-MIBG

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Introduction
Pheochromocytomas are rarely malignant, defined by the presence of cathecholamine – producing metastases. Malignant pheochromocytoma responds poorly to chemotherapy and radiotherapy. ^{131}I-MIBG therapy can be used to prolong survival, with minor side effects.
Case
A 45-years old woman known with malignant pheochromocytoma, with a long medical history, first came to our clinic in July 2012. Her diagnosis was suspected in 1999 when she experienced hypertensive crises associated with headache, palpitations and diaphoresis; investigations revealed high levels of urinary meta/normetanephrines and a 11 cm right adrenal tumor. She underwent right adrenalectomy and nephrectomy (2001). Pathology report confirmed pheochromocytoma with lymph nodes metastases. After surgery she had normal BP. In 2005 an imaging check-up revealed a liver metastasis which was surgically removed and bilateral pulmonary metastases. Thereafter, she was oligosymptomatic, with occasional palpitations, in spite of her high levels of plasmatic and urinary meta/normetanephrines. In 2012, CT and ^{123}I-MIBG scans confirmed pulmonary and mediastinal metastases, without local recurrence. We initiated treatment with a combined α/β blocker. She was then admitted for radionuclide treatment, receiving 150 mCi ^{131}I-MIBG. The concentrations of plasma and urinary meta/normetanephrines were measured after 3/6/9 months. During the follow-up we discovered an initial increase (at 3 months) in the hormonal values, possibly due to the release of catecholamines from the irradiated tumor tissues. At 9 months since ^{131}I-MIBG, the hormonal values were comparable with those before radionuclide therapy, with little decrease in lung metastases size. Despite this she remained oligosymptomatic. No side effects were observed.
Conclusion
Malignant pheochromocytoma with pulmonary metastases can be oligosymptomatic despite a long medical history, high levels of meta/normetanephrins and a poor early response to ^{131}I-MIBG treatment.

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P61

A difficult case of ectopic Cushing's syndrome due to ACTH-producing pheochromocytoma presented with normal fractionated urinary catecholamines and metanephrines

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Introduction
Ectopic ACTH secretion by pheochromocytoma causing Cushing's syndrome has been reported rarely. Here, we present a patient with ectopic ACTH-dependent Cushing's syndrome, caused by a pheochromocytoma with normal fractionated 24 h urinary catecholamines and metanephrines.
Case report
A 48-year old female patient admitted to our clinics with the complaints of severe hypertension despite receiving anti hypertensive therapy. Severe headache, malaise, nausea, vomiting, proximal muscle weakness, weight loss and palpitation episodes were the accompanying symptoms. In the physical examination, she was anxious and depressive. Her pulse was 140/min, blood pressure was 200/100 mmHg. She didn't have any typical sign of Cushing syndrome except proximal myopathy. Labaratory tests were significant for severe hypokalemia (2.5 mmol/l), hypoalbuminemia (2.6 g/dl). Her serum cortisol concentration was 63.4 μg/dl and it wasn't supressed after 1 mg and 2 days 2 mg dexamethasone suppression tests (DST). 24 h urinary free cortisol was extremely high (18980 μg/day) whereas urinary fractionated catecholamines and metanephrines were normal. Her serum ACTH was measured with IRMA and was found as 289.3 pg/ml. Our initial endocrinologic diagnosis was ACTH-dependent ectopic cushing syndrome since there wasn't any supression with HDDST, treatment resistant hypokalemia, negative pitiutary imaging and dramatic and rapidly progressing clinics. A computed tomography scan revealed a 43×37 mm tumoral mass in the left adrenal gland and PET-CT showed a 5 cm sized lesion in the left adrenal gland with high SUVmax (18.7) and hyperplasia in the other adrenal. She was underwent right adrenalectomy with Addison and pheochromocytoma protocol. After operation pathological examination was compatible with pheochromocytoma, and immunostained with ACTH extensively.
Conclusion
Ectopic ACTH-secreting pheochromocytoma is a diagnostic challenge for the clinicians. Serum or urinary metanephrines and catecholamines are very sensitive and specific tests for the diagnosis of pheochromocytoma but negative results may occur and confusion in the diagnosis.

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Expression of IGF/mTOR pathway components in human pheochromocytomas and *in vitro* inhibition of PC12 rat pheochromocytoma cell growth by mTOR inhibitors alone and in combination with the dual IGFI-R/INS-R antagonist OSI-906

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The mTOR and IGF pathways have been suggested to play a role in the pathogenesis of pheochromocytomas (PCC). mTOR inhibitors, as sirolimus (S) and everolimus (E), as well as IGF1R antagonists could be a potential novel treatment for malignant PPC.
The aim of this study was to evaluate the expression of the main components of the IGF/mTOR pathway in human PCC and to investigate the effects of the mTOR inhibitors S and E and of the IGF1R/insulin receptor (IR) blocker OSI-906, alone or in combination in a rat PCC cell model.
mRNA expression of IGF1, IGF2, IGF1-receptor (IGFR), IR subtype A and B, IGF2R, IGF-binding-proteins (BP) 1, 2, 3 and 6, mTOR, 4EBP1 and p70S6K was evaluated in 24 human PCC by quantitative-PCR. In PC12 cells, the dose- and time-dependent effect of S, E and OSI-906 and the effect of combined selected doses of S and OSI-906 on cell growth and apoptosis were tested by measurement of total DNA content and DNA fragmentation assay respectively.
In human PCC a high expression of IGF2 mRNA and an increased IRA/IRB ratio was found. No correlations between the expression of the main components of the IGF/mTOR pathway and the main clinical characteristics (age of diagnosis, the longest tumor diameter, malignancy and genetic syndrome) were observed. S, E and OSI-906 were able to suppress PC12 proliferation in a dose and time-dependent manner. After a 6 day treatment maximal inhibitory effects of S, E and OSI-906 on PC12 cell proliferation were 52, 43, and 69% respectively. S was slightly but significantly more potent than E. OSI-906 stimulated cell apoptosis (1249%). Combined treatment of S with OSI-906 had additive antiproliferative effects (25% of maximal additive effect at the combined doses tested; $P<0.001$). The results of the current study suggest the use of OSI-906, alone or in combination with mTOR inhibitors, as a potential novel treatment for patients with PCC.

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Asymptomatic catecholamine-producing tumours in Von Hipple–Lindau disease

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Introduction
Von Hippel–Lindau disease (VHLD) is an autosomal dominant neoplastic syndrome characterized by the development of multiple cancers and cists, including pheochromocytoma and islet cell tumors. Screening is mandatory for family members of index cases.
Case report
A 23-year-old male Caucasian was referred to Endocrine Department because of the recent genetic diagnosis of VHLD during familiar screening. The mutation c.482G>A(p.Arg161GIn) was identified in the exon 3 of VHL gene in heterozigoty. His mother, the index case, harboring the same mutation, was diagnosed and treated for bilateral pheochromocytoma, retinal angiomas and pancreatic cancer. His mother's monozygotic twin was also diagnosed of VHLD and submitted to bilateral adrenalectomy, because of bilateral pheochromocytoma, photocoagulation of retinal angiomas and mastectomy because of breast cancer. The same VHL mutation was identified.
The patient was completely asymptomatic and physical examination was unremarkable.
Serum normetanephrine was slightly elevated: 200 nmol/dl (Reference value (RV) <80) but with normal suppression in clonidine test. Serum metanephrine and 24 h-urinary nor- and metanephrine were normal. There was no other endocrine dysfunction. NSE was 34 μg/l (RV<16). No vascular lesions were apparent on fundoscopic examination or CNS-RMN; a 3 cm T1-hypointense and T2-hyperintense nodular lesion was found anteriorolateral to L_3 vertebral body, suggestive of paraganglioma. Renal and adrenal CT scan identified a 2.5 cm lesion in the right gland suggestive of pheochromocitoma, confirmed by MIBG hyperfixation, that did not imaged the other lesion.
After careful pre-surgical preparation right adrenalectomy and excision of the left paravertebral lesion were performed, confirming the diagnosis of pheochromocytoma and paraganglioma respectively.
Conclusion
VHLD is a rare hereditary syndrome, due to an inactivating mutation of the VHL gene, a tumor suppressor gene. Pheocromocytoma is its most common endocrine manifestation. Our clinical report highlights the need for imaging at-risk patients, since they often are asymptomatic with normal catecholamine and cathecolamine metabolites levels.

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Analysis of pheochromocytomas/paragangliomas from Eastern Slovakia

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This multi centre observational cohort study gives a view about the occurrence, clinical and laboratory presentation, localization, histological type and genetic background of pheochromocytoma (PHEO) and paraganglioma (PGL) in Eastern Slovakia. It included 28 patients (18 women +10 men), of which 23 were diagnosed to have PHEO (82.1%) and seven patients (25%) suffered from PGL with retroperitoneal, inguinal/pelvic and mediastinal distribution. Arterial hypertension was the major symptom present in 86% with slight dominance of paroxysmal form (58%). In three cases (10.7%), the diagnosis was gained after differentiation of adrenal incidentaloma in asymptomatic patients. five patients (17.8%) were classified to have malignant form of the disease. nine patients (32.1%) were confirmed to have hereditary form – of which five patients (17.8%) with familiar medullar thyroid cancer (FMTC) and mutations in RET gene classified as multiple endocrine neoplasia 2A and four patients (14.3%) with germline mutations of SDHB gene. We found relatively high occurrence of other co-morbidities: thyroid disease in 20 patients (71.4%), impairment of glucose metabolism in 11 patients (39.3%) and apart from FMTC, four patients (14.3%) suffered also from other malignancy. Together with a bigger size of the primary tumor (6.6 cm), higher concentrations of metanephrines and prevalence of extra-adrenal tumors, malignant and hereditary forms, we suppose genetic and environmental factors of Eastern Slovakia may play a role in the etiopathogenesis. However this requires a further evaluation.

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Bone and Osteoporosis

P65

***Postpartum* osteoporosis with acute evolution: case report**

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Objectives
The cases described in the literature, with *postpartum* and lactation osteoporosis, are very rare.
Material
A case report: 28 years old women, that give birth to a 3250 g weight term child, APGAR 10, breast feeding period: 3 months, with acute back pain starting the 2nd months after delivery. On the moment our evaluation she resumed breastfeeding. 3 months after delivery she came in our office with diagnosed acute vertebral fractures T8, L1 and severe bone demineralization: lumbar spine T score $= -4.7$, and femoral neck T score $= -2.7$.
Method
Clinic evaluation: back pain, no somatic sign and symptom of any disease.
We performed: total blood count, HSS, fibrinogen, rheumatoid factor, TSH, FT4, cortisolemia, intact PTH, 25 HO vitamin D, total calcemia, phosphatemia, creatinine, uree, beta 2 microglobuline, bone turnover markers: osteocalcin, crosslaps, total alkaline phosphatase, cromogranina A, serotonin, beta 2 microglobulin, immunoelectrophoresis.
Imagistic evaluation: DEXA antero-posterior technique, cranial, thoracic, abdominal and pelvic CT scan, thoracic and abdominal MRI, cervico-toracal-lumbar-sacral radiographies, breast ductal echography, bone scintigraphy.
Results
The only anomalies we found were increased bone turnover: with repeated normal calcemia and phosphatemia levels. The diagnostic of postpartum osteoporosis was made after exclusion of: primary and secondary hyperparathyroidism, severe hyperthyroidism, Cushing's disease, osteomalacia, severe vitamin D insufficiency, multiple myeloma, Paget disease, bone cancer, bone metastatic disease, breast cancer, any type of other cancer, apparent neuroendocrine tumors.
A paraneoplasic syndrome was excluded for the moment.
Periodically markers will be performed.
The patient was put on injectable bisphosphonates.
Conclusion
Postpartum osteoporosis is an exclusion diagnostic, which need active follow-up.

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The investigation of the awareness of bone health in patients with postmenopauosal in the region of Northeastern Anatolia

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Introduction
The awareness of osteoporosis is essantial of treatment. We investigated the awareness of osteoporosis in the patients with postmenopausal women in the region of Northeastern Anatolia.
Methods
Four hundred and two patients with postmenopausal women was included in this study. We detected the age of menopause, the conscience of osteoporosis in the postmenopousal period, DEXA reports, habits of regular walking, drinking of milk, and used to vitamin D supplementation.
Results
The age of menopause was 11.7 ± 8.3 years. Postmenopausal women in 90.5% were have the awareness of bone health and osteoporosis in the patients with postmenopausal. DEXA report was detected the per cent of 71.6 of the investigated patients. The percentage of regular the consumption of vitamin D and calcium were 60.5%. Unfortunately, the habits of regular walking (5 km or 10.000 steps per day), the regular consumption of milk (1.0 l per day) and used to any drugs for osteoporosis were low respectively 23.4, 0.5, and 9.4%.
Conclusions
The awareness of bone health and osteoporozis in the postmenopausal women were high in the living of Northeasthern Anatolia. Unfortunately, the percentage of preventional and therapetical intenvention for postmenoposaul osteoporosis were low. This condition may improve the effort of health personels and used to media canals.

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Baseline characteristics of Greek patients enrolled in the ExFOS study

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Introduction
ExFOS is a multinational, non-interventional, prospective, observational study to evaluate fracture outcomes, back pain, compliance and health-related quality of life in osteoporotic patients treated with teriparatide for up to 24 months. We present the baseline characteristics of the Hellenic subpopulation.
Methods
In Greece, 439 consenting patients with osteoporosis (92.3% females), suitable for prescribing teriparatide in the course of normal clinical practice, were enrolled in the study and provided medical history, clinical data, estimations on back pain and quality of life through validated questionnaires, for which descriptive statistics were calculated.
Results
These were rather elderly (mean(S.D.) age 70.1 (9.8) years (36.4% aged 75 years or older)), slightly overweight (BMI 26.7 (4.3) kg/cm^2) patients, with predisposing factors for fracture: hip fracture in biological mother (18.1%), falls in the last year (37.1%), no exercise (49.2%), current smoking (12.1%), sight problems (37.9%), immobilization for >12 months (1.6%), muscle weakness recorded as assistance

with arms when standing up from chair (41.3%). Public health insurance coverage for reimbursement of the medicine is almost complete.
Low bone mineral density with *T*-score < -3 in lumbar spine or total hip and at least one fracture in 55.1% of patients have been recorded (70.2% of patients had vertebral and 44.2% non vertebral fractures) while 21.6% had two or more fractures.
Of enrollers, 19.8% were antiosteoporotic treatment naïve, 69.5% used at least one osteoporosis/falls related medication (specifically glucocorticoids were reported by 8.9% of patients). 88.4% experienced back pain during the last 12 months while 68.1% experienced back pain at least fairly often during the last month. Moderate to severe limitation of activities was reported by half the participants with mean 4.2 (7.7) bed days because of back pain during the previous to enrollment month.
Conclusions
Greek patients enrolled in ExFOS are severely osteoporotic with increased risk of fractures and back pain. Results should be interpreted in the context of observational studies.

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From EFOS to ExFOS: any news with teriparatide prescription habits in Greece?

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Purpose
Extended Forsteo Observational Study (ExFOS), a multinational, non-interventional, prospective, observational study to evaluate fracture outcomes, back pain, compliance and health-related quality of life in osteoporotic male and female patients treated with teriparatide (TPTD), has followed European Forsteo Observational Study (EFOS) on postmenopausal women, aiming to provide more data on the effect of the extension of treatment duration from 18 to 24 months and the new indications (glucocorticoid induced and male osteoporosis). We list alongside the results recorded in Greece.
Methods
Baseline characteristics of Greek participants in EFOS are juxtaposed with those of participants in ExFOS. Data regarding by sex analysis of the latter cohort (*post-hoc* analysis) is incorporated. Descriptive comparison of the Hellenic population of EFOS and ExFOS is attempted.
Results
ExFOS enrollment speed in Greece is 45% increased compared to EFOS. Enrollers are as elderly, exhibiting equally low bone density. Profile is somewhat different between sexes. As in EFOS, ExFOS patients complain of relatively frequent, severe back pain. Currently enrolled patients smoke more (male derived increase) but are more active (higher exercise rates and less need of arms assistance to rise). Noticeably, numerically fewer patients (especially in the female population) had fracture history, especially vertebral, compared to the Hellenic EFOS cohort. Approximately one in five patients, a fraction equivalent to that observed in EFOS, had no antiosteoporotic treatment whatsoever. A numeric decrease in calcitonin and an increase in bisphosphonates use, as prior antiresorptives, can be displayed.
Conclusions
Hellenic EFOS patients share similarities with female ExFOS patients but also have noticeable differences that may indicate a relative change towards prescription in less severely affected patients. Differences observed between male and female ExFOS TPTD users may reflect distinction in osteoporosis diagnosis and treatment for males. Data are interpreted in the context of an observational setting.

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Subclinical celiac disease presented with *postpartum* low-back pain: case report

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Introduction
There are serological findings and mucosal injury similar to the classical form but no gastrointestinal symptoms in subclinical Celiac disease (CD). In this article, we present a case of subclinical CD presented with *postpartum* low-back pain, in whom we discovered severe lumbar vertebral osteoporosis.
Case report
A 35-year-old woman admitted to our outpatient clinic with severe low-back pain. The patient had given birth 5 months ago, and was breastfeeding. Upon physical examination, her height was 155 cm, weight was 45 kg, and BMI was 18.7 kg/m^2; musculoskeletal and neurological examinations were normal. The laboratory analyses results were as follows: hemoglobin 10.2 g/dl, serum calcium 7.2 mg/dl, phosphorus 2.0 mg/dl, ALP 605 U/l, 25(OH) vitamin D <5 ng/ml, and PTH 640 pg/ml. Anti-gliadin IgG and tissue transglutaminase IgA–IgG tests were found positive. The patient's DXA scan revealed L_1–L_4 lumbar vertebrae *Z*-score was -4.4. No fracture was observed in lumbar X-ray. A lower duodenal biopsy showed moderate villous blunting and cript hyperplasia. A significant increase in lamina propria infiltration by lymphoplasmacytic and neutrophilic infiltration were observed. The diagnosis of subclinical CD was made based on these findings and the patient was placed on a gluten-free diet, calcium carbonate, and vitamin D_3 treatment.
At the 3rd month follow-up visit, the patient was totally recovered from her low-back pain. Bone mineral density measurement 6 months after initiation of therapy showed a significant increase at the lumbar vertebra (*Z*-score: -0.2).
Conclusion
Development of osteoporosis may be accelerated in patients with subclinical CD due to the increased calcium demand in pregnancy. Subclinical CD should definitely be investigated in patients with *postpartum* osteoporosis. Moreover, the fact that dramatic improvement can be obtained in these patients through treatment with calcium and vitamin D should be kept in mind.

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Vitamin D receptor (VDR) gene polymorphisms and the risk of low bone mass in type 1 diabetic patients

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Osteoporosis is a common skeletal disease characterized by low bone mass and microarchitectural deterioration with increased susceptibility to fracture. Osteoporosis has a complex etiology and is considered to be a multifactorial polygenic disease. There are more than 150 genes associated with bone mineral density. Our aim was to investigate the frequency of occurrence of vitamin D receptor (VDR) – (FokI, BsmI, ApaI, TaqI) – single nucleotide polymorphisms (SNPs) in type 1 diabetic patients.
Materials and methods
We studied 62 type 1 diabetic (T1D) patients (26 men and 36 women; mean age 31.46 ± 8.55; duration of the disease 13.40 ± 7.41; HbA1c 8.25 ± 0.95%). Bone mineral density was measured by dual-energy X-ray absorptiometry. QIAamp DNA Blood Mini Kit (Qiagen) was used to purify DNA from whole blood, gene polymorphisms were detected in PCR-RFLP (restriction fragment length polymorphism) analysis. The following restriction enzymes were used to determine the appropriate polymorphism: VDR-FOKI - FokI (BseGI), VDR-BSMI - BsmI (Mva1269I), VDR-TaqI - TaqI, VDR-ApaI – ApaI. Patients with co-morbidities and conditions associated with low BMD were excluded from the study.

Results
VDR-FokI SNP was detected in 40% of cases; VDR-BsmI – in 56% of cases; VDR-TaqI – in 47% of cases; VDR-ApaI – in 38% of cases. There were 37% of homozygotes with VDR-FokI, 35% – with VDR-BsmI, 6% – with VDR-TaqI and 34% with VDR-ApaI.
Conclusion
The results of the study reflect the high frequency of vitamin D receptor (VDR) - (FokI), BsmI, ApaI, TaqI) SNPs which probably may explain the occurrence of low bone mineral density in type 1 diabetic patients.

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Bone mineral density in Iranian patients: effects of age, sex, and BMI

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Introduction
Osteoporosis is a multifactorial skeletal disease that is characterized by reduced bone mineral density (BMD). BMD values depend on several factors such as age, sex and age at menopause. The purpose of this study was to determine the prevalence and changes in BMD in Iranian patients.
Methods
Three hundred patients were selected through random sampling technique in 2009. BMD was assessed by Norland machine at the lumbar and femoral neck. Weight and height were measured through standard methods. A thorough history was taken from each patient. The data was analyzed using SPSS software version 13.0. P values < 0.05 were considered statistically significant.
Results
From among the 300 studied patients, 86.6% were female. Their mean age was 52.7 years. Their average BMI was 28.14 kg/m^2. Mean T-score at lumbar spine and femoral neck was -1.07 ± 1.19 and -1.75 ± 1.33 respectively. Mean BMD value at lumbar spine and femoral neck was 0.92 ± 0.19 and 0.77 ± 0.16 respectively. The prevalence of osteoporosis at lumbar spine and femoral neck was 33.7% and 16.7 respectively. There was a significant correlation between age, BMI and BMD values (P value <0.01). Correlation between gender and BMD value at the lumbar spine and femoral neck was not significant.
Conclusion
This study shows that ageing and low BMI are risk factors associated with bone loss. It is recommended to measure BMD and implement prevention programs for high-risk people.

Keywords: bone mineral density, BMI, age, gender
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Characteristics of the endocrine osteoporosis

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Introduction
Musculoskeletal manifestations of endocrine disorders are a heterogeneous group of disease, often giving rise to various clinical or radiological individuals. Osteoporosis is a not uncommon complication of endocrine disease. It may even be accompanied by endocrinopathy.
Aim of study
Determine mineral bone density profile of patients with endocrinopathy and define the characteristics of osteoporosis and osteopenia in these patients.
Patients and methods
Descriptive study concerning patients followed for endocrinopathy in the Service of Endocrinology and Diabetology of the University Hospital Mohamed V of Marrakech from January 2012 to January 2014.
Preliminary results
The sex ratio of patients is 0.26, with an average age of 37 and extreme ages of 16 and 73 years. 88% of patients had osteoporosis or osteopenia. 36% of them showed osteoporosis in femoral and vertebral site, and 20% at the spine. Osteopenia was found in 24% at the spine, 4% at the femoral site and 4% at the two sites. These abnormalities in bone density were revealed by the endocrine pathology in 76% of patients. The percentage of endocrinopathies responsible for its defects is as follows: 28% of hyperadrenocorticism, 28% of hypogonadotropic hypogonadism, 8% of hyperparathyroidism, 8% of hyperthyroidism.
Discussion
This work shows a high incidence of osteoporosis and osteopenia in patients treated for endocrine diseases and drove us to place the interests of systematically seek an abnormal bone density before any endocrine disorder which can cause rheumatic disorder.

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Efficacy of zoledronic acid treatment in Paget disease of bone

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Purpose
Paget disease is a disease of bone of unknown etiology with increased bone turnover that results in defective bone microarchitecture and bone deformity. Bisphosphonates are used in symptomatic Paget disease of bone. Clinical trials have shown that zoledronic acid was more effective than other bisphosphonates in treatment of Paget disease.
Methods
In this study, we retrospectively reviewed the remission and relapse statuses of 12 patients with Paget disease of bone, who were seen as outpatients between October 2011 and October 2013. We evaluated alkaline phosphates, osteocalcin, deoxypyridinoline levels measured before and at 6th, 12th, 18th months of treatment (Table 1).
Results
Pretreatment and post-treatment valus for alkaline phosphates, deoxypyridinoline, osteocalcin were as follows; 473 ± 256 U/l, 14.99 ± 7.63 mmol/l, 21.09 ± 3.18 ng/ml and 82 ± 13 U/l, 5.14 ± 1.11 mmol/l, 8.57 ± 4.31 ng/ml. Remission was achieved in all patients after treatment. The levels indicated remission continued at 12th and 18th months of treatment. There was statistically significant difference between pretreatment and post-treatment values. No statistically significant difference between the levels measured at 6th, 12th and 18th months of treatment were detected.

Table 1 Pretreatment and posttreatment results

	Basal (n:12)	**6th month** (n:12)	**12th month** (n:12)	**18th month** (n:12)
ALP (40–129 U/l)	473 ± 256	$82 \pm 13^{*}$	$67 \pm 15^{*,\dagger}$	$74 \pm 12.5^{*,\dagger,\ddagger}$
DPD (2.3–5.4 mmol/l)	14.99 ± 7.63	$5.14 \pm 1.11^{*}$	$4.90 \pm 1.18^{\dagger}$	$5.09 \pm 1.31^{*,\dagger,\ddagger}$
OC (2–15 ng/ml)	21.09 ± 3.18	$8.57 \pm 4.31^{*}$	$4.34 \pm 1.82^{*,\dagger}$	$5.45 \pm 1.35^{*,\dagger,\ddagger}$

$^{*}P<0.001$; ALP, DPD, OC values at 6th, 12th, 18th months were significantly lower than basal values. $^{\dagger,\ddagger}P>0.05$; difference between values of 6th, 12th, and 18th months were not statistically significant.

Conclusion
We recommend zoledronic acid in the first line treatment of Paget disease of bone in achieving and maintaining remission.

Keywords: zoledronic acid, bisphosphonates, bone turnover, Paget disease
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The relationship between the existence and degree of coronary atherosclerosis with the level of parathormone

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Introduction
Parathormone (PTH) is one of the major regulator of the bone and mineral metabolism. Elevated PTH levels in patients with primary and secondary hyperparathyroidism is thought to have negative effects on the cardiovascular system. In our study, we aimed to investigate a possible relationship between plasma PTH levels and coronary atherosclerosis.
Methods
Fourty-two men and 35 women, a total of 77 patients were included the study who admitted cardiology clinic because of chest pain. The patients had no previously known coronary artery disease. The patients who use a drug or have a disease which can affect calcium or PTH levels were excluded. Plasma lipids, calcium, phosporus, albumin, intact PTH and 25-OH vitamin D levels were measured from the blood samples which were taken 1 h before the angiography procedure following a 8 h fasting. The existence and degree of coronary atherosclerosis were evaluated with The Gensini score from images of angiograms. SPSS 13.0 was used for statistical analyze.
Results
When the all risk factors are evaluated we found no relationship between the existence and degree of coronary atherosclerosis and levels of PTH and 25-OH vitamin D levels. Also when we divided into tertil patients by Gensini score, we didn't find any relationship between groups. A limitation of this study was the fact that most of the patients have low Gensini score.
Conclusion
There is no relationship between the existence and degree of coronary atherosclerosis and PTH/25-OH vitamin D levels in our cross-sectional study. Other studies which consider chronic process of atherosclerosis are needed.

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What factors influenced on femoral neck bone mineral density in postmenopausal women?

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Postmenopausal osteoporosis is a condition that appears as a result of a sudden reduction in E_2 production by the ovaries. The earliest is manifested by the reduction of lumbar BMD; mostly consisted of trabecular bone. Proximal femur is built mostly of cortical bone, and so is aging more slowly, but femoral fracture more often lead to disability and death. The aim of the study was to check which from the anthropometric, hormonal and biochemical markers have the influence on the femoral neck BMD in postmenopausal women. The study included 325 healthy postmenopausal women (menopause >1 year ago) a random selected of women aged 50–60. The exclusion criteria were: smoking tobacco, HRT, ovariectomy, hyperparathyroidism, neoplasm, taking of anti cholesterol and antidiabetic drugs. BMI was calculated and waist circumference was measured. The femoral neck and total body BMD were performed using DXA method. Gynoid and android fat deposits were calculated. We had determined the concentrations of FSH, E_2, DHEAS, T, SHBG, insulin, leptin, adiponectin, IL6, TNF-α and glucose using commercial kits. HOMA. E_2:T ratio, FAI and FEI were calculated. We have shown a negative correlation between the femoral neck BMD and SHBG, and positive with body weight, BMI, % of body fat, android and gynoid fat deposits, waist, fasting glucose concentration and E_2:T ratio. The TNF α concentration correlate statistically significantly negatively with femoral neck BMD, and leptin-positively. After the multiple regression analysis we found that body weight, TNF-α, glucose concentration and E_2:T ratio are independent factors affecting femoral neck BMD in postmenopausal women. Conclusions: anthropometric factors stronger than hormonal influence on femoral neck BMD in postmenopausal women. The independent factors affecting femoral BMD is body weight ($P=0.00000$), E_2:T ratio ($P=0.00149$), TNF-α ($P=0.0172$) and glucose concentrations ($P=0.0199$).

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P76

Serum concentration of pentosidine and adipocytokines is related to fragile bone fractures in patients with type 2 diabetes mellitus

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Fragile bone fractures due to deteriorating bone quality are increased in patients with type 2 diabetes mellitus. This study aimed to measure serum levels of pentosidine and adipocytokines, e.g. adiponectin and leptin, and compare between those biochemical markers and bone mineral density of lumber in patients with type 2 diabetes mellitus. Serum concentration of adiponectin, leptin and pentosidine was measured in 19 type 2 diabetic patients (mean age $65.9+2.3$ years) and 13 normal controls (mean age $67.6+3.1$ years). Lumber mineral density was measured by dual-energy X-ray absorptiometry. Moreover, serum tartrate-resistant acid phosphatase 5b (TRAP-5b) and procollagen -1 N-terminal telopeptide (P1NP) were measured. Serum concentration of pentosidine was increased in type 2 diabetic patients. However, serum adiponectin and leptin levels were significantly decreased in type 2 diabetic patients as compared with normal control ($P<0.01$). Moreover, bone mineral density of lumber and serum concentration of TRAP-5b and P1NP were tendentiously decreased in type 2 diabetic patients compared with normal control. Especially, bone mineral density of lumber was significantly reduced in type 2 diabetic patients with lumbar bone fractures ($P<0.05$) and serum concentration of pentosidine was strongly increased in type 2 diabetic patients with lumbar bone fractures ($P<0.01$). We have investigated the relationship between bone mineral density and biochemical marker of adipocytokines and bone turnover in type 2 diabetic patients. Several investigators have reported that both adiponectin and leptin stimulated the osteoblastic activity and suppressed the osteoclastic activity, suggesting that low concentrations of adipocytokines lead to diminish bone mineral density. Our data have presented that lumbar bone mineral density, adiponectin, leptin and P1NP in type 2 diabetic patients were lower than those in normal control. In contrast, the pentosidine is reported to reduce bone quality, and to induce a bone fracture. In conclusion, high concentration of pentosidine and low concentration of adipocytokines might induce osteoporosis and fragile lumbar bone fractures in type 2 diabetes mellitus.

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P77

A girl with a hard painful swelling at the right hip: hyperphosphatemic tumeral calcinosis

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Hyperphosphatemic familial tumoral calcinosis (HFTC) is a condition characterized by an increase in the levels of phosphate in the blood (hyperphosphatemia) and abnormal deposits of phosphate and calcium (calcinosis) in in the soft tissue in the periarticular location outside the joint capsule.
Case report
This girl presented at the age of 10 years with swelling and pain in the right hip region. On examination a 10×10 cm hard, non-tender swelling with well-defined margin was felt in upper lateral part of her left thigh. Imaging the right hip revealed irregular calcified mass around the right hip mainly along the lateral aspect extending up to the upper part of the metaphysis arising mainly from the gluteus maximus extending laterally to the subcutaneous fat. Tc-99 MDP bone scintigraphy demonstrated abnormal uptake in the right gluteal soft tissue region. Investigations showed high phosphorus, normal calcium, Alkaline phosphatase (ALP), and PTH, low 25(OH) cholecalciferol. Renal function was normal. The calcified mass was totally excised and histopathology and mutations in the *FGF23* gene proved the diagnosis of HFTC. Because of elevated serum phosphate she was started on phosphate binder (sevalamer 800 mg five times daily) and nasal calcitonin twice daily in addition to dietary phosphate restriction. On this treatment for 7 years, serum phosphate ranged between 1.78 and 2.1 mmol/l with normal serum calcium and ALP concentrations. Clinical and MRI follow-up showed no evidence of recurrence and no renal or eye abnormalities nor hyperostosis for these 7 years. Linear growth was normal, (Ht SDS $=1.8$, BMI $=16.5$). She had normal pubertal development and menstruation.
Discussion
The *FGF23* gene provides instructions for making a protein called fibroblast growth factor 23, which is produced in bone cells and signals the kidneys to stop reabsorbing phosphate. Surgical removal should be complete because if a part of it is left, there is inevitable recurrence. Our case proved the efficacy and safety of phosphorus binder and calcitonin as adjuvant therapy to surgery for 7 years.
Conclusion
After removal of the calcified mass, long-term treatment of a patient with a phosphorus binder (sevalamer) and calcitonin prevented any recurrence.

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P78

Does testosteron have an effect on bone mineral density in post-menopausal women?

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Background
Osteoporosis is a common problem in postmenoausal women. There is limited data about the physiological importance of endogenous testosterone on bone mineral density (BMD) in older women is poorly understood.
Aim
The aim of this study was to evaluate association of endogeneous testosterone with BMD and BMI.
Materials-methods
This cross-sectional study included 64 patients (45–85 year) postmenopausal women; their demographic features, BMD and serum total testosteron levels and relationship between testosterone and BMD were evaluated. When the patients divided into three cathegories according to BMD; Group 1A: normal; Group 1B: osteopenic; Group 1C:osteoporotic.
Results
Serum total testosterone levels were found not to be correlated with BMD. We didn't find any differences in serum testosterone levels between three BMD groups.
Conclusion
This study suggests that endogenous androgens are influential on bone density in postmenopausal women. However, we didn't find any relationship. Effects of endogenous testosterone level on BMD is controversial.

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Renal aspects of primary hyperparathyroidism

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Introduction
Nephrolithiasis and bone disease are the most common complications of primary hyperparathyroidism (PHPT). The aim of this study was to evaluate the relationships between the existence of kidney stones, renal function and bone mineral density (BMD) in PHPT.
Description of methods/design
Biomedical evaluation, BMD measurements and renal ultrasonography were performed in a group of 75 consecutive PHPT patients aged 57.6 ± 12.7 years. The control group consisted of 47 generally healthy volunteers. 30 patients with PHPT were subsequently investigated again one year after effective parathyroidectomy (PTX).
Results
Osteoporosis occurred in 72% and nephrolithiasis or nephrocalcinosis in 60% of patients with PHPT. There was no significant difference in glomerular filtration rate (GFR), parathormone, calcemia, calciuria, serum vitamin 25(OH)D, bone turnover markers and BMD between patients with and without renal stones. However, in patients with nephrolithiasis serum $1,25(OH)_2D$ concentration was higher ($P=0.019$), phosphate concentration was lower ($P=0.009$) and only a slight tendency to a higher GFR and serum osteocalcin was observed.
The mean GFR of the whole group (88.3 ± 29.3 ml/min/1.73 m^2) was lower ($P=0.019$) than in controls (104.8 ± 25.1). 84% of the PHPT patients displayed a GFR greater than 60 ml/min/1.73 m^2 and thus above the recommended indication level for parathyroidectomy. However, even within this subgroup GFR was lower than in controls. GFR did not change following parthyroidectomy, although the severity of nephrolithiasis has decreased in many patients.
Conclusions
Nephrolithiasis does not seem to be the only cause of GFR reduction in PHPT. Since there is no certainty that the reduction in GFR in symptomatic PHPT is reversible after PTX, decisions regarding surgery should not be delayed even in mild cases. There is no clear correlation between BMD and the formation of kidney stones.

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P80

1,25-dihydroxyvitamin D_3 decreases the proinflammatory interleukin 17 serum levels

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Proinlfammatory cytokines, such as interleukin 17 (IL17) are involved in different inflammatory events causing cardiovascular diseases, osteoporosis and/or infertility. 1,25-dihydroxyvitamin D_3 (vitamin D_3) plays an immunomodulatory role and therefore, vitamin D_3 deficiency can propagate the development of autoimmune diseases, infections and cancers.
The effect of vitamin D_3 on proinflammatory cytokine levels, such as on IL17, IL6 and monocyte chemoattractant protein-1 (MCP-1) was investigated in 54 women (mean age 60 years). IL17, IL6 and MCP-1 and vitamin D_3 serum levels were measured by ELISA and chemiluminescence method respectively.
Forty-three women showed vitamin D_3 deficiency (27.45 ± 10.81 nmol/l) and 11 women had only sufficient 68.95 ± 18.44 nmol/l) vitamin D_3 levels. Women with vitamin D_3 deficiency demonstrated higher IL17 (12.5 ± 2.83 vs 11 ± 1.9 ng/ml, $P<0.49$), IL6 (26.19 ± 12.26 vs 22.68 ± 13.52 ng/ml, NS) and MCP-1 (16.92 ± 2.45 vs 16.18 ± 1.23 ng/ml, NS) levels compared with those, which women had sufficient vitamin D_3 levels. An inversely correlation was found between IL17 and vitamin D_3 levels ($P<0.026$, $r=0.3033$).
The results highlight the importance of sufficient vitamin D_3 concentration in the decrease of IL17 levels.

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P81

Factors associated with vertebral fractures in patients with primary hyperparathyroidism

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Introduction
Risk of vertebral fracture (VFx) is in part independent of bone mineral density (BMD) in primary hyperparathyroidism (PHPT). The aim of this study was to examine whether other factors, including the genotype of common polymorphisms in the calcium-sensing receptor (CASR) gene, are associated with VFx.
Patients and methods
In 266 Caucasian PHPT patients, serum calcium, phosphate, creatinine, total alkaline phosphatase, intact PTH, 25-hydroxyvitamin D and 24 h urine calcium were measured. BMD was measured by dual-energy X-ray absorptiometry (DXA) and expressed as *Z*-score at spine (*Z*-LS) and femoral neck (*Z*-FN). Morphometric VFx was identified by spinal radiograph and *CASR* A986S and R990G genotypes assessed by PCR amplification and sequencing of genomic DNA.
Results
PHPT patients with VFx ($n=100$, 37.6%) had lower serum calcium levels (10.8 ± 0.7 mg/dl) and *Z*-LS BMD (-1.0 ± 1.44), higher age (61 ± 10.1 years) and prevalence (51%) of one or two S alleles of the *CASR* A986S single nucleotide polymorphism (SNP), than those without VFx (11.2 ± 1.0 mg/dl, -0.57 ± 0.97, 57.9 ± 13.1 years and 38% respectively, $P<0.05$% for all comparisons). VFx was associated with increased age (OR 1.04, 95% CI 1.01–1.17, $P=0.017$), decreased serum calcium levels (OR 1.49, 95% CI 0.99–2.32, $P=0.05$) and *Z*-LS BMD (OR 1.8, 95% CI 1.32–2.5, $P<0.0001$) and presence of one or two S alleles of the *CASR* A986S SNP (OR = 2.27, 95% CI 1.14–4.54, $P=0.02$), regardless of confounders. The cut-offs for age, serum calcium and

Z-LS BMD that best predict VFx were 58 years, 10.8 mg/dl, and −1.0 respectively. Sensitivity (92%) and specificity (92.8%) for predicting VFx were maximal in the presence or absence of all three factors. The presence of ≥2 factors plus one or two S alleles of the *CASR* A986S SNP was associated with VFx (OR 4.71, 95% CI 2.19–10.12, $P<0.0001$), regardless of confounders.
Conclusions
In PHPT asymptomatic VFx is associated positively with age, negatively with serum calcium and spinal BMD, and with the *CASR* A986S SNP, while the R990G SNP, that has been previously associated with kidney stones in PHPT is not involved in VFx risk.

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P82

Structure of bone disease the different clinical forms of primary hyperparathyroidism

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Introduction
The main pathogenic mechanism of bone development disease in primary hyperparathyroidism (PHPT) is speeding bone resorbtion over bone formation rate.
Objective
Studying the features of bone disease in different clinical variants of PHPT.
Materials and methods
We have studied 114 patients with PGPT (average age 52.19) a general medical examination has been made. The questionnaire perfomed (with the estimate of anamnestic data, osteoporosis risk factors), the study of indicators of calcium-phosphorus metabolism (PTH, Ca, Ca^{2+}, P), bone markers (alkaline phosphatase, osteocalcin, β-CTX), sonography of the thyroid and PTG, scintigraphy PTG, bone mineral density was also examined.
Results
8 men and 106 women have been examined, 100% of men were within the age group of 50 years. 24.5% of women are of childbearing age and 75.5% of them were in the physiological or surgically induced menopause. 38.7% of patients had mild forms of PHPT, 61.3% – symptomatic PHPT (21% – visceral, bone – 17.5%, mixed form 22.8%). Low bone density was detected in 75.9% of the cases (34.5% osteoporosis, 41.4% osteopenia). In 3.5% there was detected classical Recklinghausen's osteodystrophy with multiple injuries of the skeleton. 9% of the patients were marked with pathological fractures. In 13.6% of cases of mild forms of PHPT osteoporosis was detected, osteopenia – 6.8%. Bone forms of PHPT: Recklinghausen's osteodystrophy was detected in 10%, osteoporosis - 65%, osteopenia – in 25% of cases. Mixed forms of PHPT: Recklinghausen's osteodystrophy was detected in 7.7%, osteoporosis – 61.5%, osteopenia – 19% cases. The visceral forms: osteoporosis – 25%, osteopenia – 9.5%.
Conclusion
These results suggest a high prevalence of bone disease in patients with manifested forms of primary hyperparathyroidism, and the low frequency of mild forms of PHPT.

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P83

Low-carbohydrate/high-fat diets do not have negative effects on bone density in female rats in contrast to male rats

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Ketogenic low-carbohydrate/high fat diets (LC-HFD) induce weight loss in both animals and humans. However, a number of unwanted side effects with these diets have been reported. We have previously shown in male rats that LC-HFDs negatively affect bone growth and bone mineral density, possibly due to macronutrient-induced impairments of the GH/IGF-system. Given the importance of dietary macronutrients in the regulation of bone density in male rats, in this study we investigated the effect of LC-HFD on bone density in female rats.
Female rats aged 12 weeks were isoenergetically pair-fed on a control chow diet (CH), an 'Atkins-style' LC-HFD1 (protein-content matched to chow, 78.7/19.1/2.2); and a ketogenic LC-HFD2 (low protein content, 92.8/5.5/1.7) (Percentage of metabolisable energy, fat/protein/carbohydrate) for 4 weeks. Micro–computed tomography (micro-CT) was carried out using the Scanco20 scanner, ImageJ and the BoneJ plugin was used for analysis of cancellous and cortical bone in the femur.
Female rats in both LC-HFD groups displayed lower body weight gain when compared to CH, however, this was to a lesser magnitude in female rats compared to male. Micro-CT analysis revealed no differences between controls and both LC-HFD groups in cancellous bone volume (CH: 0.3±0.08%; LC-HFD1 0.3±0.03%; LC-HFD2: 0.4±0.05%), trabecular number (CH: 6.2±0.71; LC-HFD1: 5.9±0.34; LC-HFD2: 6.6±0.18) and trabecular thickness unit (CH: 0.09±0.00 mm; LC-HFD1 0.09±0.00 mm; LC-HFD2: 0.09±0.0 mm). Analysis of trabecular structure parameters (connectivity density, structure model index and degree of anisotropy) also revealed no difference between controls and both LC-HFD groups. In addition, there were no differences in cortical thickness between control and both LC-HFD groups (CH: 0.68±0.04 mm; LC-HFD1: 0.68±0.04 mm; LC-HFD2: 0.66±0.03 mm) and in cortical bone volume (CH: 9.19±0.52 mm^3; LC-HFD1: 9.24±0.27 mm^3; LC-HFD2: 9.10±0.26 mm^3).
In contrast to our findings in male rats, LC-HFDs do not appear to have negative effects on bone homeostasis in female rats in either cancellous and cortical bone compartments.

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Teriparatide treatment in a patient with severe pregnancy related osteoporosis

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Introduction
Pregnancy or lactation related osteoporosis (PLO) is very rare. It usually occurs in the third trimester or in the early *post partum* period and manifestations are severe back pain and loss of height due to vertebral fractures. Its etiology is not well understood. Classical treatment is cessation of lactation, calcium and Vit-D supplementation and biphosphanates in chosen cases. All osteoporosis drugs are approved mainly for post-menouposal osteoporosis and reports of teriparatide treatment in this group of patients is off label worldwide. Here, we represented a case with severe pregnancy related osteoporosis to whom we started teriparatide treatment.
Case
23-year-old female patient admitted at the *post partum* 2nd week with complaints of severe back pain. She denoted that pain started in the last month of her pregnancy and persisted after labour despite calcium and Vit-D supplementation. Her BMI was 24 kg/m^2, had regular menstrual cycles, and she didn't have any risk factors for osteoporosis such as smoking, corticosteroid usage or family history. Thyroid functions, parathormone level, celiac markers, kidney and liver function tests, serum Ca, P and Vit D levels were in normal ranges. We detected multiple vertebral fractures at T5, T7, T10, T11, T12 and her total vertebrate *Z*-score was −4.2 where as femur neck *Z*-score was −1. We have initiated teriparatide therapy 20 μg/day along with 1000 mg calcium and 800 IU cholecalciferol per day. Thorocal orthosis was also prescribed. At the second month of therapy her pain was totally relieved. At the 6th month of therapy BMD was increased 15% ath the lumbar spine and we continued the therapy.
Conclusion
Effective treatment of PLO is controversial. There are some concerns about biphosphanates in premenouposal age group because of possible adverse effects on fetus. They accumulate in bone and can cross placenta despite withdrawal. In previous reports teriparatide caused increased BMD up to 36%. It can also prevent futher vertebral fractures. It can be a reasonable choice for treatment.

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The total fat mass and the fracture risk assessment: a study in 146 Romanian menopausal women

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Introduction
The fat mass (FM) is assessed by DXA, magnetic resonance, etc. One of the most accessible methods for current practice is bioimpedance.

Aim
We analyzed FM based on bioimpedance and fragility fracture risk.
Material and method
This is a transversal study in women, admitted at C.I.Parhon National Institute of Endocrinology, Bucharest, Romania. The inclusion criteria were women in menopause. The exclusion criteria were previous diagnosis of osteoporosis at DXA; previous specific therapy for osteoporosis. The fracture risk was based on left hell quantitative ultrasound (QUS: Achilles); central DXA (Lunar) providing bone mineral density (BMD); 10-year absolute fracture risk based on FRAX (risk for major osteoporotic fracture: MF, and hip fracture: HF, noted with I in case of FRAX without BMD, and II in case of FRAX with BMD). FM was expressed in percents (Tanita device). The statistical analyze used SPSS 21; statistical significance (SS) was considered at $P<0.05$.
Results
146 women were enrolled (median age 57 years, mean FM: 37%). The linear regression coefficient between FM and stiffness index (QUS) was $r=0.14$ (SS); between FM and lumbar BMD was $r=0.15$ (SS); between FM and hip BMD was $r=0.27$ (SS); between FM and femoral neck BMD was $r=0.24$ (SS); between FM and MF I, respective II was $r=-0.22$ (SS), respective $r=-0.22$ (SS); between FM and HF I, respective II was $r=-0.25$ (SS), respective $r=-0.22$ (SS).
Discussion
Despite the fact that FRAX includes BMI, this is not completely overlapped with FM. The use of neck BMD in FRAX did not influence the correlation with FM. More precise methods of FM assessment will provide more data in skeleton health.
Conclusion
Positive week but statistically significant correlations were found between FM and QUS or DXA, and negative, modest but also statistically significant between FM and FRAX risk.

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The 10-year absolute fracture risk and central DXA correlations in 505 Romanian menopausal women

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Introduction
The new tool FRAX indicated risk of fracture, using or not DXA which is the golden standard for osteoporosis diagnosis.
Aim
We analyzed the lumbar DXA correlations with 10-year fragility fracture risk probability.
Material and method
A cross sectional study in postmenopausal women was designed. They were osteoporosis free at baseline; none of them has previously been treated for osteoporosis. The anamnesis, the anthropometric parameters, as well as bone metabolism were assessed. The FRAX calculator (Romanian version) was used without bone mineral density (BMD) at femoral neck. Central DXA (Lunar Prodigy) was performed at lumbar spine. The WHO criteria were used. The statistical tests used SPSS (statistical significance was at P value <0.05).
Results
505 patients were enrolled. The meadian age was 57 years. The 10-year probability of major osteoporotic fractures was 4.5%, and for hip fractures was 1.1%. The 10-year risk increases from normal DXA group to osteoporosis. The average lumbar BMD was 1.01 ± 0.1 g/cm^2. The linear regression between lumbar BMD and 10-year major osteoporotic fractures risk was: $r=-0.2$ ($P<0.05$) respectively for hip fractures was: $r=0.2$ ($P<0.05$). The value of r in each group of women having normal DXA, or osteopenia, or osteoporosis was not statistically significant. Regardless the group of patients, the hip fracture risk was lower than major osteoporotic fracture risk based on FRAX model. If using the femoral neck BMD, the fracture risk based on FRAX was not different to the risk based on FRAX model without this value.
Discussions
Poor correlation was found between FRAX risk estimation and lumbar DXA in WHO groups. The entire cohort proved highly statistically significant value of r.
Conclusion
The use of FRAX in relationship with gold standard DXA is a complementary evaluation in order to assess the fracture risk.

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P87

Bone mineral density, bone turnover and vitamin D status in women with diabetes mellitus type 2 and healthy women with osteoporosis in menopause

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Introduction
Literature data suggests increased fracture risk in women with diabetes mellitus type 2 but the underlying mechanism is not fully understood.
Aim of the study was to analyse bone turnover parameters in women with DM2 and in healthy women with osteoporosis in menopause.
Materials and methods
There were 76 participants out of wich 36 women with DM2. Average diabetes duration was 14.48 ± 10.51 years with mean HbA1c 7.83 ± 1.75%. Osteoporosis was diagnosed by hip and spine DXA scan. Osteocalcine, β-crosslaps and 25-OH-D were determined by ECLIA method on Elecsys machine.
Results
Women with DM2 compared to healthy women with osteoporosis: age (62.75 ± 7.93 vs 63.92 ± 7.21 god; $P>0.05$), body mass index (26.61 ± 5.45 vs 25.84 ± 4.34 kg/m^2, $P>0.05$), spine bone mineral density (BMD) (0.839 ± 0.084 vs 0.801 ± 0.056 g/cm^2, $P<0.05$), total hip BMD (0.752 ± 0.109 vs 0.782 ± 0.082 g/cm^2, $P>0.05$), femur neck BMD (0.691 ± 0.085 vs 0.742 ± 0.084 g/cm^2, $P<0.05$), osteocalcin (29.98 ± 10.53 vs 33.11 ± 8.56 ng/ml, $P>0.05$), β-crosslaps (530.59 ± 225.58 vs 540.88 ± 167.16 pg/ml, $P>0.05$), 25-OH-D (39.11 ± 20.52 vs 38.85 ± 17.38 nmol/l, $P>0.05$). Vitamin D deficiency (25OHD <30 nmol/l) was found in 41.7% women with DM2 and 37.5% healthy women, without statistical significance between groups.
Conclusion
Women with DM2 have significantly lower femur neck BMD. Statistical significance between bone turnover parameters, vitamin D status and vitamin D deficiency frequency between groups was not found. Further studies of complex mechanism of increased fracture risk in women with DM2 are needed.

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The $-857C/T$ single-nucleotide polymorphism of *TNFα* gene is associated with bone mineral density in Greek peri- and postmenopausal women

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Introduction
The cytokine tumor necrosis factor alpha (TNFα) is encoded by the *TNFα* gene and stimulates bone resorption. TNFα is involved in the pathogenesis of bone loss associated with estrogen deficiency. Polymorphisms in the *TNFα* gene have been associated with bone mineral density (BMD) in different populations.
Objectives
The present study aimed to explore the influence of the single-nucleotide polymorphism $-857C/T$ in the promoter of the *TNFα* 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
200 and 17 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 −857C/T polymorphism was performed by PCR. Levels of OPG, soluble RANKL (sRANKL) and bone metabolic markers were measured.
Results
The frequencies of the genotypes of the *-857C/T* polymorphism were 57.1% for CC 40.1% for CT and 2.8% for TT. Due to the small number of women carrying genotype TT, the study population was divided into two genotype groups: CC and CT/TT. The $-857C/T$ polymorphism was significantly associated with spinal BMD. Women carrying CT/TT genotypes had higher spinal BMD than women with the CC genotype (CT/TT 0.830 ± 0.125 g/cm^2 *vs* CC 0.800 ± 0.114 g/cm^2, $P=0.03$). The association remained significant after adjustment for age, years since menopause and BMI ($P=0.046$).

Conclusions
These findings demonstrate that the functional −*857C/T* polymorphism of the *TNFα* gene may influence BMD at the lumbar spine in peri- and postmenopausal Greek women.

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State of bone metabolism in patients with urolithiasis

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Much attention is attracted increased risk of fractures in patients with urolithiasis. Study the possible relationship of pathophysiological mechanisms of osteoporosis/osteopenia and nephrolithiasis.
Objective
To assess the state of bone metabolism, vitamin D level in patients with urolithiasis compared with healthy individuals.
Methods
Were examined 58 patients with nephrolithiasis (36 women, and 22 men) and 20 healthy individuals (17 women, and three men). Exclusion criteria: primary hyperparathyroidism and other endocrine pathology, chronic renal failure, bisphosphonates and/or calcium and vitamin D in history. Group matched for age (50 ± 11.4 and 51 ± 12.7 years respectively), the number of women in menopause, renal function, carbohydrate and purine metabolism, BMI. All patients underwent a study of markers of bone turnover (b-cross laps (CTX), osteocalcin (OC)), 25 OH vitamin D (from autumn to early spring), PTH, calcium in the blood and urine daily.
Results
According to the results of significant differences in the level of PTH, 25 OH vitamin D, CTX and OC between patients with nephrolithiasis and the control group was not obtained. However, in patients with nephrolithiasis has a tendency to a higher frequency of vitamin D insufficiency in 60.3 and 36.2% in the deficit than in the control group – hypovitaminosis D in 50%, 25% deficit ($P_{X2} < 0.05$). Mean level of calcium in the blood was comparable in groups, reducing urinary calcium in both groups 15%, hypercalciuria noted only in patients with nephrolithiasis in 12%. In 30% of patients with urolithiasis recorded a slight increase in PTH levels, which was regarded as secondary hyperparathyroidism against the background deficiency of vitamin D. in the control group revealed no increase in PTH levels. Patients with nephrolithiasis 12% of cases, in contrast to the control group, marked decrease of the average OK to 8.3 ± 2.7 ng/ml at a rate of 11.0–43.0. Increasing CTX did not differ between the groups was observed in of nephrolithiasis and 10% in the control.
Conclusions
There were no differences in terms of calcium-phosphorus metabolism and bone metabolism between patients with nephrilithiasis and healthy individuals. Further studies with the definition of the BMD in comparison with the general population.

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P90

Familial hypocalciuric hypercalcemia: an important differential diagnosis from hyperparathyroidism

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Introduction
Familial hypocalciuric hypercalcemia (FHH) is a rare, benign, autosomal dominant condition usually caused by heterozygous inactivating mutations in the gene encoding the calcium sensing receptor (CASR).
Case
22-year-old woman referred to endocrinology for suspected polycystic ovary syndrome. Hypercalcemia is detected. Laboratory tests showed persistent hypercalcemia with a serum total calcium of 11.1 mg/dl (8.8–10.2), phosphorus 2.8, iPTH 101.7 pg/ml (10–65) and vitamin D 17 mg/dl (2.7–4.5). Urine calcium of 186.9 mg/24 h with a fractional excretion of calcium of 0.18% and calcium: creatinine clearance ratio (CCCR) 0.016. Parathyroid ultrasound and scintigraphy revealed no changes and MRI showed and image of 4×4 mm behind the left thyroid lobe consistent with parathyroid adenoma. Upon the diagnosis of primary hyperparathyroidism (PHPT), upper left parathyroidectomy is performed after having identified the four glands. Histological analysis showed a normal parathyroid tissue.
Persistent postsurgical high levels of calcium and iPTH prompt us to consider the diagnosis of FHH and to request a genetic study that revealed the presence, in heterozygosity, of the pathogenic mutation c.2089 G>A (*P*.Val697Met) in exon 7 of CaSR gene. Biochemical evaluation and genetic analysis was carried out on relatives, finding mild hypercalcemia, normal/high PTH and genetic mutation in her brother and father as well as in other paternal family members.
Discussion
FHH is a rare but important cause of hypercalcemia, especially in the younger population because its presentation significantly overlaps with that of the much more common PHPT with respect to almost any clinical variable except the CASR gene test. The diagnosis is important in order to avoid unnecessary therapeutic interventions.
The CCCR can help differentiate but it has its limitations related to an indeterminate range between 0.01 and 0.02 where the diseases continue to overlap. Genetic testing for mutations in the CaSR gene is the only method for confident diagnosis of FHH.

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Usefulness of serum sclerostin as a diagnostic marker of osteoporosis in a cohort of spanish postmenopausal women

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Introduction
Sclerostin, produced by osteocytes, is a potent inhibitor of Wnt signaling and bone formation. The usefulness of its determination in clinical practice is not well established.
Objectives
The aims of this study were to evaluate serum sclerostin levels in a cohort of Spanish posmenopausal women, and to analyze its relationship with bone metabolism.
Methods
We measured serum sclerostin in 97 posmenopausal women using ELISA and we also evaluated calciotropic hormones, bone turnover markers, bone mineral density (BMD), morphometric vertebral fractures, and prevalent fractures.
Results
Mean levels of sclerostin were 36.7 ± 14.4 pmol/l. We did not found a significant relationship between serum sclerostin and calciotropic hormones, bone turnover markers or BMD. In contrast, sclerostin levels were significantly lower in osteoporotic women (*n*:34) compared with non-osteoporotic women (*n*:67): 31.4 ± 11.02 pmol/l vs 39.57 ± 15.27 pmol/l, $P = 0.007$. In the ROC curve analysis to evaluate the usefulness of sclerostin as a marker for high risk of osteoporosis, the area under the curve was 0.678 (95% CI: 0.565–0.791, $P = 0.004$). A concentration of 35.03 pmol/l or lower showed a sensitivity of 70.6% and a specificity of 54% to detect an increased risk of osteoporosis. However, we did not found differences in sclerostin levels according to the diagnosis of morphometric vertebral fractures or the history of prior fracture.
Conclusions
In summary, circulating sclerostin levels were decreased in Spanish women with postmenopausal osteoporosis but serum sclerostin had limited usefulness as a diagnostic marker of osteoporosis.

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Increased osteoporotic fractures' risk in elderly patients with lower sodium levels

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Background
Low serum sodium levels were associated both in experimental studies and in clinical practice with increased prevalence of osteoporosis, due to decreased

bone mineralization and increased osteoclastic activity. On the other hand, hyponatremia – independent of osteoporosis – is associated with fracture occurrence.
Objectives
To assess the relationship between serum sodium levels and osteoporotic fractures.
Patients and methods
160 patients (7M/153F), aged 62.2±11 years were retrospectively assessed. DXA measurement was performed in 133 patients. In all the other 27 patients, DXA was not considered mandatory due to presence of osteoporotic fractures (femoral neck in 18 patients and distal radius in nine patients). Serum natremia was measured in all patients.
Results
41 out of 160 patients (25.6%) showed various types of osteoporotic fractures (vertebral fractures, femoral neck or distal radius fractures). Patients with osteoporotic fractures were significantly older (71.6±9.5 vs 58.9±11 years, $P<0.001$, *t*-test) and had significantly lower serum sodium levels (139.2±3.1 vs 141.1±5.32 mmol/l, $P=0.01$, *t*-test) compared to patients without osteoporotic fractures. Prevalence of hyponatremia (serum Na <135 mmol/l) was higher in patients with osteoporotic fractures (four out of 41 – 9.7%) as compared with patients without fractures (six out of 119 – 5.04%), but without reaching statistical significance ($P=0.28, =\chi^2$ test).
In patients with DXA assessment, $n=27$ showed normal bone mineral density (group A), $n=55$ showed osteopenia (group B) and $n=51$ patients showed osteoporosis scores (group C). Prevalence of hyponatremia tends to be lower in groups A and B (1/27–3.7 and 2/55–3.6%) than in group C (4/51–7.8%).
Conclusion
We suggest measurement of sodium serum levels in elderly people at risk of osteoporotic fractures.

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The effects of recombinant human TSH on selected bone markers in the follow-up of patients treated for differentiated thyroid carcinoma

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Introduction
TSH seems to play direct role in bone metabolism. TSH receptors are expressed on osteoblasts and osteoclast precursors. Osteocalcin (OC) is well known marker of bone formation, whereas collagen type I crosslinked C-telopeptide I (CTX) is marker of bone resorption. Sclerostin is a protein, recently found to inhibit bone formation, while parathormone (PTH) inhibits sclerostin production. The aim of the study was to estimate sclerostin, OC, CTX and PTH levels after recombinant human TSH (rhTSH) injections in patients treated for thyroid cancer.
Patients and methods
The analysis included 33 postmenopausal women in age from 43 to 73 years (mean age 52±10.7 years, mean±S.D.) who underwent surgery for papillary thyroid carcinoma (PTC) and were treated with suppressive doses of L-thyroxine, undergoing stimulation with exogenous rhTSH (Thyrogen Genzyme) during routine evaluation for cancer remnants. Serum sclerostin, OC, CTX and PTH concentrations were measured. A blood sample was drawn from each patient at baseline and 5 days after rhTSH administration.
Results
A significant rise in CTX in serum after TSH injection was observed ($P=0.013$). Serum sclerostin and osteocalcin levels did not change significantly over the time ($P>0.05$).
Serum PTH level started to rise along with TSH but a significant increase of PTH was only reached on day 5. There was no significant correlation between TSH concentration and the various parameters measured.
Conclusions
The acute TSH administration results in an increase of CTX but does not affect sclerostin and osteocalcin levels.

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Influence of osteoporosis risk factors on extensive suppression of bone metabolism during antiresorptive therapy

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Introduction
Some patients develop excessive bone metabolism supression during antiresorptive therapy. Low remodelling rate enables increase in tissue mineralisation density and homogenicity of bone trabeculae. Increase in density makes microdamage more likely. Increased homogenicity provides less resistance to spread of the micro-cracks and slowed remodelling slows down removal of microdemage. All this leads to increased bone fragility.
Aim
To establish whether excessive suppression of bone resorption and entire remodelling process depends on osteoporosis risk factors.
Materials and methods
Prospective, longitudinal study with 200 female participants with diagnosed osteoporosis of was done. Average age was 62.3±9.74 years. Osteocalcine (OC) and β-crosslps (β-CTx) were determined before therapy and three months after initiation of antiresorptive therapy. Group 1: OC and β-CTx below reference range; Group 2: β-CTx below reference range; Group 3: normal levels of OC and β-CTx; Group 4: increased bone metabolism during therapy. Analysed risk factors were: age, smoking habits, menarche, menopause, labours, lactation, fragile fracture, height reduction, osteoporosis in family.
Results
There were no statistically significant differences between age, menarche, menopause ($F=0.794$, $P=0.623$), fragile fracture ($F=1.315$, $P=0.27$), height reduction ($F=0.408$, $P=0.751$), smoking habits ($F=0.1.17$, $P=0.322$), fragile fracture in relatives ($F=0.572$, $P=0.638$). There was statistically significant difference among groups: group 2 had longer menopause ($F=5.171$, $P=0.002$) and longer duration of lactation ($F=2.954$, $P=0.033$). Group 4 had longer generative period ($F=2.839$, $P=0.039$) and fewer children ($F=2.682$, $P=0.0$)
Discussion and conclusion
Osteoporosis risk factors may have the role in excessive suppression of bone metabolism during antiresorptive therapy. further studies of this problem are needed to enable identification of patients who may develop excessive bone turnover suppression as a potential adverse effect of antiresorptive therapy.

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Osteoporosis in young male secondary to cancer treatment: case report

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Introduction
Children undergoing treatment for cancer are prone to several long-term endocrine complications, which can permanently affect bone tissue.
Case report
A 25-year-old man was diagnosed with right maxillary sinus rhabdomyosarcoma at the age of 5. He was submitted to chemotherapy – intrathecal methotrexate + prednisolone and i.v. vincristine + actinomycin + ifosfamide – and submaxillary + cervical radiotherapy, 60Gy. At the age of 12, he was referenced to Endocrine Rehabilitation Clinics. Laboratory: IGF1 102 ng/ml (<p3), TSH 7.4 mIU/ml (0.3–4.2), T_3 120 ng/dl (80–200), FT_4 0.8 ng/dl (0.9–1.7). He started levothyroxine (50 μg/day). Adrenal and gonadal axes were normal. Insulin-tolerance-test showed GH insufficiency. Auxology: height 139 cm (p10), predicted adult stature (PAS) 170 cm; bone age 9 years; Tanner stages P2G2, testicular volume (TV) 5 ml. According to national criteria back then, he wasn't eligible for somatropin treatment. Pubertal spurt wasn't achieved. At the age of 14 growth velocity remained in p3 (−2SD). He reached P5G5, TV 25 ml when he was 17. PAS wasn't achieved. One year later he performed bone mineral density (BMD) scan – *T*-score: lumbar spine (LS) −3.1, femoral neck (FN) −1.9. Calcium and cholecalciferol were started, without improvement. At the age of 21 he showed: LH 1.7 mIU/ml (>8), FSH 2.0 mIU/ml (>10), total testosterone 324.8 ng/dl (160–730) and dihydrotestosterone 253 ng/dl (300–850). Testosterone enanthate 250 mg/ml monthly was started. Despite correct replacement and appropriate physical activity, 2 years later he presented with *T*-score: −3.8 (LS), −2.1 (FN). He was still showing IGF1 of 79 ng/ml (<p3) so he started somatropin. Currently (25-year-old) he exhibits *T* - score: −3.6 (LS), −2.3 (FN).

Conclusion
Our patient developed growth hormone insufficiency secondary to radiotherapy. This contributed to impaired bone mass acquisition. Methotrexate and glucocorticoids' adverse effects on bone are usually reversible. Peak bone mass should already been reached when partial gonadal axis insufficiency was established. It's important to identify the risk of endocrine complications in order to treat these patients properly.

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Jaw osteonecrosis in a patient with postmenopausal osteoporosis on antiresorptive treatment

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Postmenopausal osteoporosis is a common condition affecting many women. Management of postmenopausal osteoporosis involves the administration of vitamin D, calcium and antiresorptive agents. The long-term management of postmenopausal osteoporosis with antiresorptive agents may present some dangers and adverse effects such as bone necrosis or atypical bone fractures.
Case report
The aim was to describe the case of a female patient with postmenopausal osteoporosis who presented with acute pain in the jaw and was diagnosed with jaw osteonecrosis.
A female patient, aged 68, presented with acute pain in the left side of the mandible. X ray examination revealed jaw osteonecrosis. The patient had postmenopausal osteoporosis. She had presented with premature menopause at the age of 40 and had been treated with oestrogens. Thereafter alendronate had been administered. Alendronate was discontinued and a year later denosumab was initiated. The patient presented with acute jaw pain lasting for a month. As she had periodontitis, she attributed the pain to this affliction. CT examination revealed osteonecrosis of the mandible. Antibiotics were administered and oral hygiene with chlorhexidine was instructed. The patient adhered and the pain improved, not ceasing, however, completely.
Jaw osteonecrosis is a rare adverse effect of antiresorptive therapy for postmenopausal osteoporosis. It is known to occur especially in patients with poor oral hygiene and may be related to excessive suppression of bone turnover. It can cause diagnostic difficulties as the intense pain may be attributed to various dental problems that the patient may be experiencing. Management of jaw osteonecrosis involves the administration of antibiotics, oral hygiene with chlorhexidine and in some cases surgical removal of the affected bone.

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Assessment of *OPG/RANK/RANKL* gene expression levels in peripheral blood mononuclear cells after treatment with hormonal replacement therapy and tibolone in patients after menopause with osteopenia or postmenopausal osteoporosis

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The aim of the reported study was to assess gene expression levels of the OPG/RANK/RANKL system in peripheral blood mononuclear cells (PBMC) after tibolone and hormonal replacement therapy (HRT) administered to patients with oestrogen deficiency symptoms and osteopenia or postmenopausal osteoporosis.
Material and methods
74 women after menopause, aged 45–71 years, were enrolled into the study and randomly assigned to different medical therapies: HRT and tibolone. Patients of the control group received only calcium and vitamin D_3 supplements. Measurements of β-CTX (C-terminal Telopeptide of type 1 Collagene), osteocalcin, of RNA expression in PBMC cells, serum alkaline phosphatase concentrations, as well as of total serum calcium and phosphate levels and of their 24 h urine excretion rates were evaluated at every visit (at baseline and after 3, 6 and 12 months). Densitometry of the left hip and of the lumbar spine (LS) was done at baseline visit and after 12 months.
Results
The differences in gene expressions of *RANKL* and *RANK* were not significant during the study period and did not differ significantly between the groups. No *OPG* gene expression was observed in PBMCs of patients in any of the studied groups and at any time point. In the tibolone group, positive, statistically significant relationships were found between the differences in *RANK* and *RANKL* expression and changes of bone mineral density (BMD) of LS and femoral neck. The tendency of positive correlations ($P=0.051$) was observed between *RANKL* and *RANK* gene expression and total hip BMD in the patients treated with HRT. In a control group a significant positive correlation and a tendency of positive correlation were demonstrated, respectively between the alterations of *RANKL* gene expression and changes of trochanter BMD and between the changes of *RANK* gene expression and differences in osteocalcin concentrations ($R^{\wedge 2}=0.193$; $P=0.078$).
Conclusions
Both tibolone and HRT do not seem to cause significant changes in gene expression levels of *OPG/RANK/RANKL* in PBMCs during the first 12 months of treatment.

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Assessment of OPG and RANKL serum levels after treatment with hormonal replacement therapy and tibolone in patients after menopause with osteopenia or postmenopausal osteoporosis

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The aim of this study was to evaluate quantitative changes in OPG and RANKL proteins after tibolone and hormonal replacement therapy (HRT) administered to patients with oestrogen deficiency symptoms and osteopenia or postmenopausal osteoporosis.
Material and methods
A total of 74 women after menopause, aged 45–71 years, patients of the Outpatient Clinic of Osteoporosis of the Military Teaching Hospital in Lodz, were enrolled into the study. The patients were randomly assigned to different medical therapies: HRT and tibolone. Patients of the control group received only calcium and vitamin D_3 supplements. Measurements of β-CTX (C-terminal Telopeptide of type 1 Collagene), osteocalcin, RANKL, OPG, alkaline phosphatase concentrations in serum (sALP), as well as total, 24 h calcium and phosphate levels in serum and urine were carried out in material collected at every visit (at baseline and after 3, 6 and 12 months of therapy). Densitometry of the left hip and the lumbar spine (LS) was done twice (at baseline visit and after 12 months).
Results
The observed changes in bone mineral density (BMD) between the groups, as well as within each group, were statistically insignificant. In none of the three groups were any significant differences in serum levels of the bone turnover markers, OPG and RANKL during the whole study period. A significant negative correlations were demonstrated between the differences in osteocalcin concentrations and BMD changes of LS, femoral neck and total tip in the tibolone receiving patients. Additionally, in the same group of patients, negative, statistically significant relationship was found between the alterations of β-CTX concentrations and the differences in LS BMD.
Conclusions
Both tibolone and HRT do not seem to cause any significant changes in OPG and RANKL protein serum levels during the first 12 months of treatment.

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Effect of estroprogestagen treatment on bone mineral density and concentration of osteoprotegerin in girls with Turner syndrome

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Background
Osteoprotegerin (OPG), a component of the RANKL/RANK/OPG pathway, can inhibit bone resorption by affecting osteoclastogenesis. Estrogens deficiency is associated with decreased expression of OPG and increased osteoclast activity, and thus can lead to disorders of bone remodeling.
Objective
To analyze relationship between serum OPG and bone mineral density (BMD) in patients with Turner syndrome (TS) subjected to estroprogestagen (EP) treatment.
Material and methods
The study included 44 patients with TS, aged between 16 and 28 years. All the patients were characterized by short stature, lacked any signs of puberty and primary amenorrhea, and had no history of treatment with EP, GH and anabolic preparations. Therefore, they represented natural model of clinical hypoestrogenism. We monitored hormonal parameters (TSH, fT_4, FSH, LH, E_2, T) of the participants, along with their bone turnover marker levels (BALP, Ntx) and bone mineral density (BMD). Furthermore, OPG concentration was determined prior to and after 6 months and 2 years of EP treatment.
Results
The average increase in BMD amounted to $7.5\% \pm 10.9$ and $6.6\% \pm 9.5$ g/cm^2 after the first and the second year of treatment respectively. However, BMD documented after 2 years of hormonal treatment did not differ significantly from its pretreatment level. The baseline concentration of OPG amounted to 4.52 ± 0.79 pmol/l, and its concentrations measured after 6 months and 2 years of EP treatment equaled 6.47 ± 1.64 pmol/l ($P < 0.01$) and 4.39 ± 0.78 pmol/l ($P > 0.05$) respectively.
Conclusion
Although increased endogenous synthesis of OPG is considered a therapeutic target in patients with reduced bone mineral density, we did not observe significant increase in BMD after 2 years of estroprogestagen treatment, and concentration of OPG returned to its pre-treatment levels. This suggests that estrogens exert limited effect on osteoprotegerin expression.

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Bone mineral density in girls with functional hypothalamic amenorrhea subjected to estroprogestagen treatment: a 4-year prospective study

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Introduction/objective
To evaluate the effects of estroprogestagen therapy (EP) on the mineral bone density (BMD) of girls with functional hypothalamic amenorrhea (FHA).
Design
Prospective observation of 78 FHA girls subjected to 4-year EP therapy (Group A) and 50 controls (Group C).
Methods
Anthropometric measurements (height, body weight) were taken for all participants along with baseline values of hormonal parameters and bone turnover markers: serum concentration of the bone fraction of alkaline phosphatase (BALP) and urine concentration of cross-linked n-telopeptide of type I collagen (Ntx), and BMD measurements. Follow-up measurements of hormonal parameters, BALP and Ntx were performed after 6 months of EP treatment in patients belonging to Group A. BMD measurements were carried out on a yearly basis, starting 12 months after the initiation of EP therapy.
Results
Six-month EP treatment resulted in a marked increase in estradiol levels and a significant decrease in BALP and Ntx. The relative increase in BMD was highest after the second year of treatment. Based on the dynamics of BMD changes during the first year of treatment, we identified a Subgroup A1 with no or insignificant reactions to the treatment. It was characterized by significantly higher baseline BMD and markedly lower baseline Ntx compared to the patients who responded to 1-year therapy well (subgroup A2) or extremely well (subgroup A3). Further follow-up proved, however, that subgroup A1 did not differ significantly from the other patients in terms of the long-term prognosis for BMD normalization.
Conclusions
EP therapy is effective in the treatment of BMD disorders associated with FHA.

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Calcium and Vitamin D metabolism

P101

Predictive value of early phosphate measurement in post-thyroidectomy hypocalcemia: a prospective study

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Background
The aim of this study is to compare the value of phosphate measures, which may predict the development of hypocalcemia in the early post operative period following total thyroidectomy, to iPTH and Ca measurements.
Metods
In this prospective study, patients who underwent total thyroidectomy in our clinic between March 2012 and April 2013, independent of diagnosis were included in a consecutive manner. Venous blood samples for calcium (Ca^{2+}), phosphate (PO_4^{3-}) and iPTH measurements were taken from the study patients $\sim$24 h before surgery and shortly after the patient was brought back to their beds on the surgery ward. Calcium measurements were made immediately when symptoms of hypocalcemia developed or 24 h postoperatively in symptom free patients and at day 5 postoperatively to evaluate late hypocalcemia.
Results
120 patients who underwent total thyroidectomy in our clinic were included in this study. Values of PO_4^{3-} over 3.5 mg/dl was found to be the most sensitive parameter in predicting postoperative hypocalcemia with a rate of 59.09%. The specificity of this parameter was found to be 67.1%. The sensitivity and specificity of a measured iPTH value below 10 pg/ml was 29.55 and 92.11% respectively. The sensitivity and specificity of a measured value Ca levels <8 mg/dl was 18.18 and 94.74% respectively.
Conclusion
In light of our findings, we suggest that phosphate levels measured in the early postoperative phase of total thyroidectomy, can be used to predict the development of hypocalcemia. Phosphate measurement can be used as an alternative particularly in centers where iPTH measurement cannot be performed.

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P102

The effect of FGF23 on renal phosphorus handling is dependent on PTH secretion

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Background
Chronic hypophosphataemia due to renal phosphorus wasting results in bone disease (rickets and osteomalacia). The principal regulators of renal phosphorous handling are parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23). X-linked hypophosphatemic (XLH) rickets is the most common genetic disorder of renal phosphorus wasting; acquired disorders include tumour-induced osteomalacia (TIO). The aims of this study were: i) to assess the clinical utility of FGF23 measurement in congenital and acquired disorders of phosphate homeostasis and ii) to assess the relative effects of PTH and FGF23 on renal phosphorus handling.
Methods
55 subjects consented to participate in this study. They were subdivided into three groups: i) FGF23-mediated ($n=15$) including congenital hypophosphataemia ($n=13$) and TIO ($n=2$); ii) non-FGF23-mediated ($n=38$) including a variety of metabolic bone disorders; and iii) two cases of XLH with hypoparathyroidism post total parathyroidectomy for severe hyperparathyroidism. Fasting morning serum and urine samples were obtained. Tests included FGF23, TmP/GFR, ionised calcium, 25OHD, PTH, and creatinine.

Results
Subjects with FGF23-mediated disease had higher FGF23 and lower TmP/GFR than the non-FGF23-mediated disease group. In the FGF23-mediated group significant inverse correlations were noted between TmP/GFR and ionised calcium ($r=-0.659$, $P=0.01$) and FGF23 ($r=-0.595$, $P=0.026$). In the non-FGF23-mediated group significant inverse correlations were noted between TmP/GFR and ionised calcium ($r=-0.514$, $P<0.001$) and PTH ($r=-0.506$, $P=0.001$). Adjusting for ionised calcium, PTH, and creatinine the relationship between TmP/GFR and FGF23 approached significance ($r=-0.581$, $P=0.061$) in subjects with FGF23-mediated group, but not in the non-FGF23-mediated group ($r=-0.063$, $P=0.721$). In XLH patients with hypoparathyroidism post total parathyroidectomy, TmP/GFR was normal despite marked elevation in FGF23 with undetectable PTH
Conclusions
FGF23 levels are a determinant of TmP/GFR in congenital and acquired disorders of FGF23 excess, but the effect of FGF23 on renal phosphorus handling is dependent on PTH secretion, even if there is a disorder in FGF23 production.

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P103

Screening of genes involved in cAMP-mediated signalling in a large Italian series of patients affected with Albright hereditary osteodystrophy and/or Pseudohypoparathyroidism

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The term pseudohypoparathyroidism (PHP) defines a heterogeneous group of rare, related and deeply impairing metabolic diseases due to end-organ resistance to the actions of PTH, associated to molecular defects at the GNAS locus. Different subtypes of PHP have been described based on the existence of additional clinical features, such as resistance to other hormones acting via GPCRs and Albright's hereditary osteodystrophy (AHO). Recently, the detection in a small subset of PHP patients with no GNAS defects of genetic defects associated with diseases showing a phenotypic overlap with PHP, such as acrodysostosis (ACRDYS) and brachydactyly-mental retardation syndrome (BDMR), challenged the distinction of these complex disorders. Despite the high detection rate of genetic and epigenetic defects by currently available molecular approaches, about 30% of PHP patients still lack a molecular diagnosis, hence the need to screen patients negative for GNAS genetic or epigenetic defects also for chromosomal regions and genes associated to diseases that undergo differential diagnosis with PHP. To this purpose, we screened our AHO/PHP patients negative for *GNAS* point mutations, structural rearrangements and imprinting defects (sporadic or genetic-based), for the presence of genetic mutations at *PRKAR1A* ($n=58$), *PDE4D* ($n=18$), as well as for deletions affecting the subtelomeric region of the long arm of chromosome 2 ($n=38$). We detected 2 missense mutations at the *PRKAR1A* gene, 2 intronic mutations at the *PDE4D* gene and two deletions involving the chromosome 2q37 and overlapping with previously described rearrangements affecting this subtelomeric region. In silico analysis predicted a pathological effect for all genetic defects found in our patients.
These findings highlight the complexity in performing an accurate diagnosis of PHP, further confirming the molecular and clinical overlap among these disorders, as well as the pivotal role of the cAMP pathway in the development of the AHO phenotype.

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P104

Neurological manifestations of vitamin D deficiency, is there any significant clinical correlation?

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Objective
The objective of this study was to investigate the correlation between the neurological manifestations of vitamin D deficiency and the levels of 25(OH)D and bone profile.
Methods
We conducted a case series study in patients with osteomalacia who were followed up at King Abdulaziz Medical City, Jeddah, between January 2011 and December 2012. We collected information on demographic data, etiological factors for vitamin D deficiency, clinical presentations (typical and neurological), and radiological findings. *T* test was used to determine whether there was a correlation between the neurological manifestations of vitamin D deficiency and vitamin D levels and bone profile. A *P* value <0.05 was considered significant.
Results
Sixty patients were enrolled in the study. Atypical presentations included progressive muscle weakness (proximal more than distal) in 73% of the cases and gait disturbances in 61.7% of the patients. There was no significant correlation between neurological manifestations and the bone profile or vitamin D levels. Significant correlations existed only between the inability to walk and the levels of serum calcium and phosphate, with *P* values of 0.043 and 0.037 respectively.
Conclusions
Neurological manifestations of vitamin D deficiency are not correlated with the levels of 25(OH)D or bone profile.

Key Words
vitamin D deficiency, vitamin D, proximal myopathy, bone profile.
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P105

Brown tumor in a patient with ectopic mediastinal parathyroid adenoma: a case report

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Introduction
Brown tumors are rare focal giant-cell lesions that arise as a direct result of the effect of parathyroid hormone on bone tissue in some patients with hyperparathyroidism.
Case
A 55-year-old Saudi woman was admitted to King Abdulaziz University Hospital (Jeddah) with a complaint of anterior maxilla mass of one month duration. Her medical history was unremarkable.
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 (reference range, 50–136 IU/l); corrected serum calcium, 3.2 mmol/l (reference range, 2.12–2.52 mmol/l); and intact parathyroid hormone, 120 pmol/l (1.6–6.9 pmol/l). A provisional diagnosis was made for hypercalcemia due to hyperparathyroidism. Technetium thallium (99mTc-201Th) subtraction scintigraphy (Sestamibi scanning), which demonstrated a single, ectopic anterior mediastinal parathyroid adenoma. Magnetic resonance imaging (MRI) of the thorax showed a mediastinal parathyroid adenoma. Treatment was initiated by hydration with normal saline and intravenous biophoshante until normalization of the patient's serum calcium level.
Initially the patient underwent extirpation of the mass and curettage of the bone under general anesthesia. Histological sections showed multiple giant cells consistent with Brown tumor of primary hyperparathyroidism. The patient was readmitted after 2 weeks, and she underwent mediastinal parathyroidectomy by median sternotomy. The lesion was histopathologically diagnosed as a parathyroid adenoma. The post-operative course was uneventful and the patient was discharged on the 6th post-operative day without complications. The results of postoperative laboratory tests were normal.
Conclusions
Owing 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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P106

Biochemical response and imaging changes in 99mtc-mibi in patiens with primary hyperparathyroidism treated with Cinacalcet

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Introduction
Treatment with Cinacalcet results in decreased uptake of radiopharmaceutical (because of decreased secretory activity of parathyroid glands as shown by previous studies in secondary hyperparathyroidism). This effect has not been studied in patients with primary hyperparathyroidism (PHPT).
Objective
Evaluate clinical and MIBI scintigraphy uptake changes of adenomas in patients treated with Cinacalcet.
Patients and methods
We collected data from patients between years 2009 and 2013. We evaluated demographic and analytical parameters. Scintigraphy changes (qualitatively and semiquantitatively) of 16 patients (four patients have a negative one). We determined: uptake rate (%) mean and maximum uptake images during early (15 min of contrast administration) and late (2 h) and reassessed after treatment with Cinacalcet, minimum period of 3 months.
Results
27 patients receive treatment with Cinacalcet, ten men and 17 women, diagnosis age 65 years. Initial profile: calcium, 11.34 ± 1.12 mg/dl; phosphorus, 2.62 ± 0.38 mg/dl; and PTHi, 260.96 ± 190.04 pg/ml. Dose 30 mg in 80 and 60 mg in 20%. We found significant decrease in calcium ($P < 0.001$) and PTH levels ($P < 0.05$). After treatment, calcium 9.62 ± 1.19 mg/dl, phosphorus 2.77 ± 0.63 mg/dl; and PTHi, 119.9 ± 179.41 pg/ml. One patient discontinue because of intolerance.
Qualitative scale 75% of analyzed patients decreased uptake on the scan performed after treatment, 12% obtained same. One case negative in baseline scan then located adenoma in post-treatment scan. Quantitative scale shows a trend to statistical significance but no differences between pre- and post-assessments, maximum and mean or early and late phase uptake.
Conclusions
Treatment with Cinacalcet is effective reducing calcium levels in PHPT patients. Cinacalcet seems to decrease scintigraphy uptake of parathyroid adenomas in patients with PHPT. Further studies should evaluate the clinical relevance of this finding.

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P107

Reversal heart failure secondary to severe hypocalcaemia

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Introduction
Clinical manifestations of hypocalcaemia vary from very mild and asymptomatic biochemical abnormality to severe life-threatening disorders. Heart failure due to hypocalcaemia is refractory to conventional treatment. Many clinicians may be unaware of hypocalcaemia associated with heart failure, since it is often ignored. Hypocalcaemia heart failure is a rare and potentially reversible disturbance, The decompensated heart failure is rapidly reversed by aggressive calcium supplementation.
Case report
We report a 16-year-old female with previous history of convulsions who developed cardiac failure due to hypocalcaemia. Echocardiography showed left ventricular dilatation, global hypokinesia, mild systolic dysfunction (ejection fraction 35%), moderate pericardial effusion. Low serum calcium mild hyperphosphateamia, elevated alkaline phosphates, and elevated PTH. After aggressive treatment of hypocalcaemia by calcium infusion–vitamin D supplementation, signs and symptoms of heart failure dramatically improved with almost full recovery of left ventricular function (67% ejection fraction after 16 days of the initial echo) The patient was discharged under stable conditiond with calcium carbonate, calcitriol.with follow-up clinically and echocardiographically stable.
Conclusion
We conclude that in a young patient a thorough investigation for heart failure is never complete without looking for endocrine and metabolic causes. Serum calcium level should be monitored in every patient with cardiac failure and hypocalcemia should be considered in patients with refractory heart failure.

Keywords
Heart failure; hypocalcaemia pseudo hypoparathyroidism
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P108

Novel mutation of the *AIRE* gene in Iranian patients with autoimmune polyglandular syndrome type 1

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Autoimmune pollyendocine type 1 (APS1) is a rare inherited autosomal recessive disorder. Typical symptom appears in within the first decade of life and followed by adrenocortical insufficiency, mucocutaneous candidiasis, Addison's disease, and hypoparathyroidism. The clinical phenotype of APECEP is depends on mutations in autoimmune regulator gene (AIRE) which mapped to chromosome 21q22.3. We analyzed *AIRE* gene in subject to identify *AIRE* gene variants and may new mutations to facilitate the genetic diagnosis of APS1 in Iranian patients. We detect a novel insertion mutation, Lys50AsnfsX168 in exon 2 of one of our patients using bidirectional sequencing. We also identified known mutations Arg139Stop, Arg257Stop, and Leu323SerfsX51 in compound newly discovered mutation. According our report analysis of *AIRE* gene establishes a useful diagnosis method in patient with incomplete or unusual clinical presentation.

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P109

Effect of vitamin D concentration on pregnancy, health of pregnant women, and newborn

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Introduction
In pregnant women there is a twofold increase in synthesis of calcitriol, i.e. the active metabolite of vitamin D. Literature data point to adverse effects of vitamin D deficiency during pregnancy both for pregnant woman and foetus. Polish data on the effects of vitamin D deficiency in this group are scarce.
Aim of the study
The aim of this study was to evaluate the relationship between vitamin D3 concentrations in pregnant women on health of pregnant women and newborns.
Patients and methods
The study included 109 healthy pregnant women, aged 21–40 years, (30.5 ± 4.9 years). 60 of women completed a questionnaire on the course of pregnancy, childbirth and child health. Women were divided into three groups: those with sufficient serum vitamin D3 – above 30 ng/ml, with vitamin D3 insufficiency – 25(OH)D concentrations in the range of 20–30 ng/ml and vitamin D deficiency (< 20 ng/ml).
Results
Insufficient concentrations of vitamin D deficiency are common in Polish pregnant women. Optimal vitamin D concentrations were found only in 16% of women in winter and in 47% in summer ($P < 0.03$). Bacterial vaginosis was significantly more common in the group of women with vitamin D deficiency ($P < 0.005$), whereas there was no effect of vitamin D level on the incidence of gestational diabetes, pre-eclampsia and the method of labour. There was no relation between concentrations of vitamin D during pregnancy and parameters determining size of a newborn. There was an increased incidence of respiratory tract infections in children whose mothers had been vitamin D deficient.
Conclusions
i) Vitamin D deficiency in pregnancy is common and particularly severe in winter months. ii) Vitamin D deficiency in pregnant women contributes to development of bacterial vaginosis, and increased frequency of respiratory infections in a child, thus confirming the role of vitamin D in prevention of infections.

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P110

A case of post-operative hypoparathyroidism

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Case history
A 41-year-old lady had Total Thyroidectomy in 2007 for a large multi-nodular goitre. Post-operatively, she was hypocalcemic with mild inappropriately low Pth levels. She was treated with high dose α-calcidol and calcium supplements but the response was suboptimal. Following introduction of teriparatide, serum calcium has been improving to between 1.90 and 2.06 mmol/l. She continues on high dose α-calcidol.
Investigations
Corrected calcium range in the 6 months preceding pre-teriparatide, 1.71 1.93 mmol/l. Corrected calcium range in the 6 months post T/t, 1.90–2.10 mmol/l. Serum magnesium, normal.
Results and treatment
Teriparatide, 20 mg s.c. daily. α-Calcidol 4–15 mg OD; currently 8 mg OD. Thyroxine currently 200 mg OD.
Conclusions and points for discussion
Post-operative hypoparathyroidism following thyroid surgery occurs in 1–4% of patients. Treatment options include high dose α-calcidol and in the occasional patient use of synthetic human parathormone which could be the truncated hormone teriparatide (1–34) or intact hormone preotact (1–84). 1000 patients are members of Hypoparathyroidism UK of which six are on teriparatide and ten are on preotact. Cost of treatment with either is comparable.
References
Oxford Textbook of Endocrinology, BNF2013. Hypoparathyroidism UK, Prof. William Fraser.

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P111

Bone and vitamin D status in young male patients with relapsing kidney lithiasis and hypercalciuria

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Introduction
Idiopathic hypercalciuria is a risk factor for nephrolithiasis. Both renal stones and hypercalciuria are often associated with lower bone mineral density (BMD), but the relationship between these modifications is not completely understood. We aimed to evaluate some metabolic particularities possibly related to relapsing nephrolithiasis in young male patients.
Methods
We performed a cross-sectional study including a group of 30 young male patients with relapsing nephrolithiasis (group RN) and a group of 30 healthy, age and BMI matched controls (CTR). We evaluated calcium and phosphate in serum and 24 h urine samples, bone remodelling markers alkaline phosphatase (AP) and osteocalcin and lumbar and hip BMD.
Results
We observed higher values of serum calcium ($P<0.05$) and 24 h urinary calcium excretion ($P<0.001$) in the RN group. Although in the normal range, parathyroid hormone (PTH) and AP were also higher in the RN group ($P<0.01$). 25OH-D3 was lower than normal in many volunteers from both RN and CTR groups. However, 25OH-D3 was significantly lower in the RN group (20.2 ± 11.9 vs 30.4 ± 14.4 ng/ml, $P<0.01$). BMD, *T*- and *Z*-scores were lower in the RN group in both the lumbar ($P<0.01$) and hip ($P<0.05$) regions. 25OH-D3 levels were inversely correlated with PTH and directly correlated with lumbar and hip BMD in the RN group.
Conclusions
Young male patients with hypercalciuric RN seem to have lower BMD and higher bone turnover. Vitamin D deficiency may well be another environmental modification caused by modern life and favouring relapsing nehrolithiasis. Higher PTH levels related to vitamin D deficiency may contribute to bone demineralization in certain cases. Although still controversial, antiresorptive therapy, such as bisphosphonates, together with vitamin D repletion may be a logical therapeutic solution to prevent bone loss and also decrease calciuria and RN risk.

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P112

Surgery for primary hyperparathyroidism: a 10 years single-centre experience

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Objective
To describe the clinical characteristics and post-surgical outcome of our primary hyperparathyroidism case series.
Methods
A retrospective cohort study of primary hyperparathyroidism patients who underwent surgery in the last 10 years in our centre. The medical records were reviewed to extract data. A statistical descriptive analysis was performed using mean and s.d. for continuous variables and percentages for qualitative variables.
Results
Sixty-three patients were included (83% women). Mean age: 58.2 ± 15. 78% of patients were referred for altered blood tests, 20% for clinical symptoms, and 2% for imaging findings. Serum biochemistry tests results are showed in Table 1. 52.3% of patients had associated nephrocalcinosis, 47.6% high blood pressure, 31.7% osteoporosis, 20.6% renal insufficiency, and 17.6% altered hydrocarbon metabolism. One patient was diagnosed with multiple endocrine neoplasia. 99mTC was performed in 37 patients: 73% showed focal uptake. 54 patients underwent an ultrasonographic test of which 29.6% showed a parathyroid disorder. 44% of patients fulfilled the clinical criteria for surgery. Of these, 56% were asymptomatic at the time of the surgery. Anatomic pathology results were as follows: 74% adenoma, 23% hyperplasia, and 3% carcinoma. The recovery rate was 88.7% (87% of adenomas and 93% of hyperplasias). The post-surgical permanent complications were: 4.8% hypoparathyroidism and 4.8% vocal paralysis. Patients without a pre-surgery scintigraphy had more complications compared to those who had it (30.8 vs 8.3%).

Table 1 Serum biochemistry test results.

	Pre-surgery	Post-surgery	References
Serum calcium (mg/dl)	11.82 ± 1.54	9.28 ± 0.49	<10.2
PTHi (pg/ml)	304.82 ± 350.7	53.75 ± 50.89	<65

Conclusions
Primary hyperparathyrodism is more common in women over the age of 50. Post-surgical complications and recovery rates in our cohort are similar to other published series. Recovery is not associated with pathology. 99mTc is the most useful diagnostic procedure and is associated with fewer post-surgical complications.

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P113

Severe hypomagnesemia due to long-term PPI use

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A 73-year-old woman, admitted to emergency room due to generalized tonic–clonic seizures. She had a previous history of muscle cramps and paresthesia for 4 months. She had a medical history of peptic ulcer and she was taking omeprazole for 7 years. Her laboratory evaluation showed marked hypomagnesemia (<0.4 mg/dl normal ranges: 1.7–2.55 mg/dl) and hypocalcemia (6.83 mg/dl and normal ranges: 8.8–10.2 mg/dl) with extremely low urinary Ca and Mg excretion (<1.22 mg/day and 0.01 g/day respectively). Her vitamin D level was normal (34.47 IU) and PTH was increased (129 pg/ml and normal ranges: 15–65 pg/ml) in accordance with the secondary hyperparathyroidism.

Symptoms resolved with the i.v. supplementation of calcium gluconate and magnesium sulphate. However despite high levels of oral replacement, Mg levels remained low. With omission of omeprazole 3 months after the admission her ion levels returned to normal without any replacement. We report a case of hypocalcemia and hypomagnesemia due to long-term proton pump inhibitor intake.

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P114

A novel mutation in *GATA3* gene in HDR syndrome

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The combination of hypoparathyroidism, sensorineural deafness and renal dysplasia, named HDR syndrome, is a rare disease. Heterozygous abnormalities of *GATA3* gene are associated with this syndrome. Here we report a novel heterozygous mutation, c.255_256ins4 (GTGC), in *GATA3* gene. A 41-year-old man was diagnosed as having idiopathic hypoparathyroidism and has been treated with 1α-hydroxyvitamin D3 and calcium carbonate. Three years later, he had a hearing impairment and revealed sensorineural deafness by audiogram. Renal ultrasonography did not show abnormality in the kidney. His son was also diagnosed with hypoparathyroidism and hearing deafness due to seizure episode at age 12 years. His son's renal ultrasonography showed right kidney aplasia. DNA analysis was performed in his son. Sequenced analysis identified a novel mutation, c.255_256ins4 (GTGC), in the *GATA3* gene. A boy showed classical triad of HDR syndrome. But his father had only two clinical feature of HDR syndrome (hypoparathyroidism and sensorineural deafness), besides he did not complain of a hearing impairment when diagnosed with hypoparathyroidism. Taking into consideration this clinical heterogeneity, screening of *GATA3* gene mutations is worthwhile for diagnosis and genetic counseling, when patients have hypoparathyroidism and deafness.

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P115

Correlations of vitamin D level with hormonal and biochemical parameters in polycystic ovary syndrome

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Objective
To investigate the level of 25(OH) vitamin D (25(OH)D) and correlation between 25(OH)D level and hormonal-biochemical parameters in polycystic ovary syndrome (PCOS).
Materials and methods
Thirty-three patients diagnosed with PCOS and 42 age and BMI matched control group admitted to Erzurumm Regional Training and Research Hospital from May to October were included in the study. Serum total testosterone (TT), free testosterone (fT), 25(OH)D, DHEAS, LH, FSH, TSH, cortisol, 17αOH-progesterone, fasting glucose, and insulin levels were evaluated after 12 h fasting. HOMA-IR (fasting glucose level×fasting insulin/22.5) was calculated.
Results
Serum 17αOH progesterone and 25(OH)D levels were significantly lower in PCOS group ($P<0.01$). Serum LH, LH/ FSH TT, FT, insulin, ACTH, and DHEAS levels were significantly higher in PCOS group ($P<0.01$). There was statistically significant negative correlation of 25(OH)D levels with PCOS, LH/FSH, TT, fT, DHEAS, and FGS. There was no statistically significant correlation between 25(OH)D levels and age, BMI, and insulin resistance.
Conclusion
The results of this study indicated that vitamin D deficiency is highly prevalent among women with PCOS independent of BMI. We also demonstrated that vitamin D deficiency was correlated with hyperandrogenism in PCOS women. Low serum 25(OH)D levels might exacerbate PCOS symptoms. Large intervention trials are needed to evaluate the effect of vitamin D supplementation on hormonal and clinical parameters in PCOS women.

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P116

Cardiovascular view and QT interval in primary hyperparathyroidism

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Introduction
Primary hyperparathyroidism (pHPT) is the unregulated overproduction of parathyroid hormone resulting in abnormal calcium homeostasis. The prevalence has been reported to be ∼21 cases/100 000 person-years. The mean age at diagnosis has remained between 52 and 56 years with female-to-male ratio 3:1. In ∼85% of cases, pHPT is caused by a single adenoma, in 14% of hyperplasia and 1% is caused by malignant diseases. Association between pHPT and cardiovascular manifestation is well known for many years. Increased cardiovascular mortality rates were reported in many studies. Changes in serum calcium level have impact on duration of QT interval. QT interval duration was inversely associated with the serum total and ionized calcium. Data from the Third National Health and Nutrition Examination Survey suggests that shortened and prolonged QT – interval durations, even within a reference range, are associated with increased mortality risk in the general population.
Methods
Aim of our study was to compare ECG changes especially QT and RR interval using 24 h ambulatory electrocardiography in patients with pHPT and controls. A total of 41 (39 women and two men) patients with pHPT and 41 control subjects of similar age, body weight and cardiovascular risk factors was enrolled in this study. The age of participants ranged from 28 to 83 years (mean age was 55 years), the serum calcium level was from 2.62–3.06 mmol/l (reference range (RR) 2.25–2,65 mmol/l), the level of an intact parathormone was between 61.4 and 441 ng/ml (RR 65 ng/ml). A control group consisting of 41 patients (40 women and one men), the age of control group ranged from 40–75 years (mean age was 57.5 years), the serum calcium level was in the reference range from 2.25 to 2.55 mmol/l, the level of the intact parathormone was from 48.01 to 60.5 ng/ml.
Results
We observed statistically significant data - changes in QT interval and RR interval as follows: QT max. (886.122 vs 749.317; P 0.0013; median 850 vs 773; $P<0.001$) , QTc max. (992.122 vs 806; $P<0.001$; median 910 vs 781; P 0.004), QTc min. (89.5366 vs 100.854; $P<0.002$; median 90 vs 104; P 0.0015), RR average (754.658 vs 794.366; P 0.0133), RR max. (4573.41 vs 2418.37; $P<0.0113$; median 1445 vs 1063; P 0.0004), and RR min. (351.902 vs 470.268; P 0.0003).
Conclusion
There are resulting data about a statistic impact of hypercalcaemia in primary hyperparathyroidism at QT max., QTc max. and QTc min., and all RR intervals (RR min., RR aver, and RR max.). In accordance with published data we confirm a statistic significance shortening of QT interval, especially QTc min. interval in patients with pHPT, but conflicting data about impact of hypercalcaemia at QTc max. and QT max. interval, there we observed prolonged QT intervals in patients with pHPT compared with controll group. RR average and RR min. intervals were shorter in observed group compared to controlls. Changes in QT interval (shortening or prolongation) are associated with higher cardiovascular or total mortality in general population.

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P117

New vitamin D less-calcemic analog affects human bone cell line and cultured vascular smooth muscle cells similar to other analogs

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Vitamin D receptors (VDRs) are expressed in bone and vascular cells which also respond to vitamin D treatment by modulation of cell proliferation measured by DNA synthesis and energy metabolism measured by CK specific activity. We have previously observed that vitamin D-related compounds target several genes

which affect cell proliferation, including mRNA expression of estrogen receptor (ER)α, ERβ, VDR, 1α hydroxylase of 25OHD3 (1OHase) and 12 and 15 lipoxygenases (LOs) measured by real-time PCR. In the present study we compared our newly synthesized analog, 1α,25-dihydroxy-9-methylene-19-norvitamin D3 (JK152 (JK)) on bone and vascular cells to other non-calcemic vitamin D analogs. Human bone cell line $SaSO_2$, dose-dependently responded to JK by increased DNA synthesis and stimulated CK specific activity similar to CB 1093 (CB) and EB 1089 (EB) (50–80 and 40-80% respectively compared to 60–80% by JK). JK also inhibited DNA synthesis in primary human vascular smooth cells (VSMC) dose-dependently similarly to CB and EB (80–50% compared to 75–60% by CB). VSMC expressed 12LO, 15LO, ERα, ERβ, VDR, and 1OHase mRNA. Daily treatment for 3 days with JK, CB and EB stimulated 12LO and 15LO mRNA expression (35% by JK, 0% by CB and 250% by EB of 12LO and 35% by JK, 230% by CB and 35% by EB of 15LO). JK stimulated ERα (150% by JK, 220% by CB and 190% by EB) with no effect on ERβ. Finally, JK stimulated VDR (200% by JK, 220% by CB and 190% by EB) but not 1OHase. Collectively, the effects of JK in bone and vascular cells closely resemble those of CB or EB. Hence, our data indicate that the novel vitamin D non-calcemic analog JK behaves similarly to other analogs in human cultured cells, thus paving the way to its potential use *in vitro and in vivo.*

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P118

The relationship with plasma calcium levels, metabolic syndrome, and risk parameters in overweight and obese Turkish women

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Introduction
Obesity prevalance is rapidly increasing all over the world and become a serious health problem. There is a significant correlation between serum calcium levels and body fat mass. It was indicated that when plasma calcium levels increase, BMI decrease however, insulin, total cholesterol, and triglycerides levels increase. In this study, it was investigated the relationship between plasma calcium levels and cardiovascular risk factors and metabolic syndrome parameters in Turkish overweight and obese female patients.
Materials and methods
4749 overweight and obese women were evaluated retrospectively. 872 overweight (BMI 25–30 kg/m^2) and 3877 obese (BMI >30 kg/m^2) patients who applied to Obesity Outpatient Clinic, Departmant of Internal Medicine, Istanbul Faculty of Medicine, Istanbul University were evaluated, anthropometric and biochemical parameters were measured. Patients were divided three category according to plasma calcium levels. Groups were compared with one-way ANOVA. $P<0.05$ was accepted as significant.
Results
There were no significant correlation between serum calcium levels and body weight, body fat mass, and fat distirbution. Plasma calcium levels significantly associated with cardiovascular risk parameters. In addition, metabolic syndrome indicators and risk parameters were also significantly correlated except high waist circumference.
Discussion
Our findings indicate that high serum calcium levels associated with obesity-related complication parameters. High-risk situation may occur when serum calcium levels high. Elevated calcium levels reflect a metabolic risky situation. It should be cautious to prevent complications while using high-content calcium diets for obese patients treatment.
Keywords
Obesity, serum calcium levels, insulin resistance, metabolic syndrome, cardiovascular risk factors.
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P119

Levels of vitamin D in patients with various endocrine disorders

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Introduction
The important aspect of vitamin D (vitD) sufficiency is the impact of chronic diseases and medications, which disturb the metabolism of vitD. Bone pathology is common in diseases of the endocrine system, so the determining the status of vitD in various endocrine diseases and comparing it to otherwise healthy controls is of particular interest.
Materials and methods
The study included 16 patients with type 2 diabetes mellitus (T2DM), 23 patients with primary hyperparathyroidism (PHPT), 68 patients with Cushing's disease (CD), and 22 patients with acromegaly. In selection of control group patients ($n=163$, 30M/133F; mean age 48.5 ± 18 years) we used exclusion criteria: presence of primary hyperparathyroidism, secondary or tertiary hyperparathyroidism on the background terminal chronic renal failure, hypercortrosolism, blood creatinine level of more than 100 mmol/l or GFR <60 ml/min per 1.73 m^2, intake of active vitD metabolites within 1-month prior the blood test. Our lab takes part in the international program of external control and standardization of vitD in the blood (DEQAS, UK) and utilizes a total 25(OH)D (LIAISON, DiaSorin) assay.
Results
We observed a significantly lower levels of vitD in patients with T2DM (15.3 ng/ml), acromegaly (15.7 ng/ml), and CD (16.6 ng/ml) compared to a group of healthy patients (19.9 ng/ml). In patients with PHPT vitD levels were not statistically different from the control group.
Conclusions
The study shows a high prevalence of vitD deficiency not only in groups of patients with chronic diseases, but also in control patients. The absence of significant variations in the concentration of vitD in patients with PHPT may be due in part to the vitD supplementation in the treatment of osteoporosis, which is one of the main manifestations of the disease. Further research is needed to provide the reasons for the high prevalence of vitD deficiency described in endocrine diseases.

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P120

Calcium metabolism in a child with type 1 diabetes mellitus and familial Mediterranean fever

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Introduction
Recent studies demonstrate decrease in vitamin D3 level and bone mineral density in more than 50% of type 1 diabetes (T1DM) patients. It is also suggested that vitamin D deficiency in familial mediterranean fever (FMF) patients may trigger the disease flare. These patients are at high-risk of other autoimmune diseases, as well as described combination of FMF, celiac disease, and autoimmune thyroiditis. However, there are only two case reports on combination of FMF and T1DM. We present a case of concomitant T1DM and FMF in a child and evaluate the features of bone metabolism in this rare pathological combination.
Case report
A 5-year-old boy, suffering from T1DM about 3 years, was diagnosed with FMF ~1.5 years ago. Within a year after the manifestation of T1DM he experienced recurrent abdominal and bilateral lower extremity pains, making it difficult to compensate glucose as the child was malnourished. Ca^{2+} was 1.15 mmol/l, vitamin D3 4.0 ng/ml, and PTH 42.9 pg/ml were identified. FMF was diagnosed by identifying two gene mutations in the compound heterozygous state V726A/M680I. D hypovitaminosis was found. Celiac disease was excluded. The patient is currently on insulin and colchicine therapy, supplemental vitamin D3 and calcium. During this treatment pain gradually improved, allowing for appropriate correction of diabetes. On vitamin D3 treatment 500 IU/daily for 1 year, serum level improved to 15.64 ng/ml, Ca^{2+} was 1.12 mmol/l, Ca urine/daily 1.63 nmol/l.
Conclusions
Taking into consideration that the average annual duration of Sunshine Hoursin Armenia is 2350, and number of cloudy days is 42, we can assume that a low level of vitamin D3 in this child was due to a combination of FMF and T1DM. Further studies with larger patient populations are needed to investigate if the vitamin D deficiency in patients with T1DM and FMF is more profound compared to isolated T1DM or FMF.

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P121

Retrospective evaluation of patients with primary hyperparathyroidism in Konya Meram Faculty of Medicine

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Introduction
Primary hyperparathyroidism (PHP), is generalized with calcium, phosphate, and bone metabolism disorder due to increased PTH secretion. It's common in fifth and sixth decades. Nowadays, it's widely detected by measurement of blood calcium and may be presented with minimal or no symptoms.
Design
102 patients with PHP admitted to Department of Endocrinology, between years of 2008–2013 were analyzed.
Results
The sample included 80 females and 22 males. Mean age was 54.6 ± 10.9. Mean level of serum calcium was 12.03 (9.4–18.4) mg/dl (normal range 8.9–10.3), phosphorus was 2.7 mg/dl (normal range 2.4–4.7), PTH was 364.5 pg/ml (12–88), and 24 h urine calcium was 470 mg/24 h (100–300). In ultrasonography, adenoma was detected in 66 of patients. Average adenoma size was 15.76 mm (min size 6 mm and max size 60 mm). Parathyroid MIBI scintigraphy was performed in 90 patients and in 70 of them adenomas were detected. Adenomas were most frequently in right inferior localization (52.7%). Bone densitometry was performed in 60 patients and 33 osteoporosis and 20 osteopenia were detected. 22 patients had history of nephrolithiasis. Preoperatively, fine-needle biopsy was performed for thyroid nodule/adenoma differentiation and PTH washing was analysed in ten patients. The average value was 2235 ± 1488 pg/ml. Minimally invasive surgery (MIS) was performed in 33 patients, open surgery (OS) was performed in 56 patients. In pathological evaluation, 71 of 89 patients had parathyroid adenoma, 14 of them had parathyroid hyperplasia, and three of them had parathyroid carcinoma.
Conclusion
The majority of our patients (63%) were treated with OS. MIS has lower morbidity than OS in literature. If we cannot define the adenomas with radiologic and scintigraphic methods, fine-needle biopsy and PTH wash can be used. In this way, more patients may have the chance of MIS.

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P122

Frequency of BsmI polymorphism of vitamin D receptor gene and its association with 25-hydroxyvitamin D levels

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Introduction
Vitamin D deficiency has become a major public health problem. It's known that the effects of vitamin D are made by its receptors. VDR gene polymorphisms in susceptibility to different diseases demonstrated in many studies. The polymorphisms of VDR are ApaI, TaqI, FokI, and BsmI. BsmI is the most extensively studied polymorphism. In our study, the aim is to show the frequency of VDR BsmI gene polymorphisms and to show the relationship between polymorphisms and vitamin D levels.
Design
All population were divided into two groups which are 100 osteoporotic and 100 non-osteoporotic. The demographic characteristics were recorded. In blood samples vitamin D, calcium, phosphorus, and alkaline phosphatase; in urine samples urinary calcium, urinary creatinine were studied. In addition, approximately 2 cc of peripheral blood sample was taken for DNA isolation and VDR BsmI polymorphisms were studied by real-time PCR method and comparisons were made between the groups.
Results
In all of population BB genotype 17%, Bb genotype 50.5%, and bb genotype 32.5% were found. In osteoporotic grup BB genotype 16%, Bb genotype 48%, and bb genotype 36% were found. In non-osteoporotic grup BB genotype 18%, Bb genotype 53%, and bb genotype 29% were found. There was no statistically significant difference between groups. The level of vitamin D was 18.10 ng/ml in BB genotype, 17.08 ng/ml in Bb genotype, and 16.34 ng/ml in bb genotype. There was no statistically significant difference between genotypes.
Conclusion
There was no statistically significant relationship between genotypes and vitamin D levels and also was no statistically significant relationship of VDR gene BsmI polymorphisms between two groups. Serious vitamin D deficiency was detected in both groups and the whole population.

Keywords
Vitamin D receptor gene, BsmI, vitamin D, polymorphism.
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P123

Correlation between 25-OH vitamin D3 and TSH concentration in population over 65: preliminary report

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Introduction
Active metabolites of vitamin D have pleiotropic influence on whole body.
Aim
The aim of the study was evaluation of the correlation between vitamin D3 and TSH values in population over 65.
Materials and methods
94 patients admitted to diagnosis on Geriatric Department entered the study. People with age above 65 were included to research and divided on two groups according to sex. The material samples were obtained from patients in the morning during routine sampling. The concentration of 25-OH vitamin D were determined by ELISA. The obtained data were statistically analyzed using STATISTICA. $\alpha = 0.05$.
Results
The examined group consist of 26 men (27.66%) and 68 women (72.34%). The average age of whole group was 77.55 ± 6.76 years. The average age of a group of men was 75.96 ± 6.51 years and groups of women 78.16 ± 6.80 years ($P = 0.1460$). The average concentration of 25-OH vitamin D3 in the study population was 14.18 ± 5.60 ng/ml in men and 15.85 ± 6.36 ng/ml in women 13.55 ± 5.19 ng/ml. The average value of TSH in the study group was 1.82 ± 1.28 μIU/ml in men and 1.41 ± 0.64 μIU/ml in the group of women 1.98 ± 1.43 μIU/ml. There were no statistical significance observed in women group in relation to 25-OH vitamin D3 and TSH concentration and between TSH concentration and 25-OH vitamin D3 in the whole group. There was observed statistically significance negative correlation between 25-OH vitamin D3 and TSH in analyzed group of men ($R = -0.43$; $P = 0.0329$).
Conslusions
Current studies showed negative correlation between 25-OH vitamin D3 and TSH concentration in group of men while it is not observe of women. The future researches are necessary in order to obtain accurate results.

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P124

Correlation among arm circumference index, 25-OH vitamin d3 concentration and lipid profile in patients over 65 years: preliminary study

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Introduction
Anthropometric parameters such as: waist circumference, hips circumference, or arm circumference allow to find a correlation between the obesity and the risk of some metabolic disturbances (for example arm circumference index of upper part indicates the level of protein storage in the body).
Aim
The aim of the study was to assess the correlation among the arm circumference index, concentration of 25-OH vitamin D3 and lipid profile parameters in patients over 65.
Materials and methods
94 patients over 65 years of age hospitalized in the Department of Geriatrics were enrolled to the study. Results of biochemical parameters were red from the patients' medical records. Arm circumference was measured in accordance with generally accepted method. The obtained data were statistically analyzed using STATISTICA with $\alpha = 0.05$.
Results
The group consists 68 women 72.34, and 26 men 27.66%, with average age as 77.55 ± 6.76 years, The mean value of arm circumference in analyzed group was 28.84 ± 4.31 cm, mean concentration of 25-OH vitamin D3 in the studied group was 14.18 ± 5.60 ng/ml, total cholesterol 184.39 ± 52.12 mg/dl, LDL cholesterol 109.93 ± 41.31 ng/ml, HDL cholesterol 50.29 ± 18.22 ng/ml, and triglycerides 128.87 ± 74.02 mg/dl. There were no statistical significance observed in current study between the circumference of the arm and the concentration of 25-OH vitamin D3 in the analyzed group of patients ($R = 0.16$; $P = 0.1399$). We did not observed any statistical significance between arm circumference and total cholesterol ($R = 0.11$; $P = 0.3452$), arm circumference and HDL cholesterol ($R = 0.15$; $P = 0.1764$) either. There were observed statistically significant negative correlation between arm circumference and HDL cholesterol ($R = -0.31$; $P = 0.0041$). In addition statistical significant positive correlation was observed between arm circumference and triglyceride levels ($R = 0.31$; $P = 0.0041$).
Conclusion
The study indicates that the measurement of arm circumference is an easy and fast method which allow the assessment of lipid profile disorders in a group of patients over 65.

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P125

First seizure presentation in an elderly woman with primary vitamin D deficiency: a case report

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Introduction
Vitamin D insufficiency is common in older people and is associated with several disorders related to aging such as osteoporosis, which leads to a significantly increased risk of bone fractures. This deficiency is more common in Mediterranean countries than in Northern European countries. Hypocalcemic seizures resulting from vitamin D deficiency are rare in adults, and fractures caused by seizures without evidence of direct trauma have not yet been reported.
Case presentation
A 63-year-old Turkish woman was brought to the emergency department after having a first seizure, right forearm fracture without trauma. Her vital signs were normal. Chvostek's and Trousseau's signs were positive. Other physical examination was normal. Brain computerized tomography (CT) and brain magnetic resonance imaging (MRI) were normal. Her medical history included subtotal thyroidectomy. Her calcium level of 5.8 mg/dl and phosporus level of 2.8 mg/dl, and albumin level was 3.8 g/dl (3.5–5.2 g/dl). PTH level was 224 pg/ml, 25 (OH) vitamin D level was 2.5 ng/ml, alkaline phosphatase (ALP) level was 189 U/l, bone alkaline phosphatase level was high. Urinary calcium excretion was low. Blood urine nitrogen (BUN), creatinine, sodium, potassium and magnesium levels were normal. An electrocardiogram showed a normal sinus rhythm with a QTc of 405 ms. The patient received i.v. calcium gluconate. The patient was diagnosed with primary vitamin D deficiency. Vitamin D3 drops 50 000 IU/week were given to the patient during 8 weeks; calcium carbonate/ vitamin D3 effervescent tablets were also administered. A BMD scan was osteoporosis. Bisphosphonate treatment was postponed because of severe osteomalacia. One month after starting vitamin D supplementation, serum 25-hydroxyvitamin D increased to a level of 28 ng/ml and PTH decreased to a level of 119 pg/ml. Serum calcium was measured at 8.5 mg/dl and phosporus at 4.2 mg/dl, within normal ranges. During hospitalization no seizures were observed
Conclusion
It is important to check for calcium levels in older patients who present with non-febrile seizures.
Keywords
Hypocalcemic seizure, vitamin D deficiency, elderly patient, bone fracture.
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P126

Primary hyperparathyroidism presented with peripheral brown tumor in the oral cavity: a case report

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Brown tumor is a non-neoplastic lesion which resulting from abnormal bone metabolism caused by hyperparathyroidism. We report a rare case of peripheral brown tumor related with primary hyperparathyroidism which simulating a peripheral giant cell granuloma of the jaws.
Introduction
PHPT occurs in a setting of excessive parathyroid hormone (PTH) secretion which resulting in hypercalcemia.
Case report
A 50-year-old man was admitted to Samsun Oral Medicine Hospital for evaluation of an oral cavitiy lesion. In physical intraoral examination, there was a sessile swelling on the anterior region of the maxilla, in $27 \times 16 \times 13$ mm diameter. The lesion was surgically removed and histopathological analysis was reported a giant cell tumor.
Blood analysis demonstrated PTH level of 355 pg/ml (normal range: 15–65). Serum calcium and alkaline phosphatase levels were also upper than normal limits, whereas phosphorus level was lesser. The patient was referred to our outpatient clinic of Endocrinology and Metabolism of Samsun Training and Research Hospital. Neck ultrasonography revealed a solitary lesion on the right parathyroid region. Tecnesium-99 m MIBI imaging detected a mass nearby inferior right thyroid gland, compatible with a parathyroid adenoma.
Discussion
Bone involvement of PHPT is usually seen in the ribs, clavicles, pelvic girdle, hand and the mandible. The jaw bones are commonly affected by brown tumors in PHPT. Peripheral manifestation of brown tumor on the oral cavity is rare, the clinical appearance simulates peripheral giant cell granuloma. The brown tumor is a kind of giant cell lesion and appears as multiple expansive osteolytic lesions of the bone. The clinical diagnosis is made based the associacion with PHPT.
Conclusion
We reported a rare case of peripheral brown tumor associated with PHPT simulating a peripheral giant cell lesion.

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P127

VDR gene polymorphisms in Alzheimer's disease: pilot study

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Aggravation of the symptoms of Alzheimer's disease may also underlie the functioning of receptors associated with calcium and vitamin D. Therefore, it seems reasonable to study the correlation of polymorphisms of vitamin D receptor (VDR) and calcium receptor (CASR) with symptoms of AD. Alzheimer's disease, vitamin D deficiency and osteoporosis often coexist in the patient. Research suggests that vitamin D deficiency is much more frequent in the patients with AD. Expression of *VDR* gene occurs in a neuronal and a glial cells. VDR belongs to the nuclear receptor superfamily and acts as a ligand activated transcription factor.
During the project it was selected a 40 patients and a group of 40 healthy volunteers. There are many polymorphisms in the *VDR* gene. In the present work we focused on assessing the prevalence of four of them relating to the regulation of expression of this gene: TaqI, ApaI, FokI and BsmI.
Distribution of all polymorphisms were obtained according to Hardy–Weinberg low (ApaI: $\chi^2=2.54$, $P=0.1111$, TaqI: $\chi^2=1.21$, $P=0.2412$, BsmI: $\chi^2=0.57$, $P=0.4490$, and FokI: $\chi^2=1.23$, $P=0.2680$).
We didn't observe any significant differences in the distribution of individual genotypes of the VDR polymorphisms in patients with Alzheimer's disease compared to control group.
Project requires further research with a larger group of patients and control group.
The project was funded by the National Science Centre, grant number. UMO-2011/01/B/NZ7/00656.

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P128

Cinacalcet hydrochloride more efficiently controls serum calcium levels in mild-asymptomatic primary hyperparathyroidism without surgery criteria, as compared with surgical cases

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Context
Primary hyperparathyroidism (PHPT) is a common endocrine disease, characterized by the chronic elevation of serum calcium (Ca) levels induced by a long-standing increase of PTH concentrations. PHPT includes mild-asymptomatic and symptomatic forms. Cinacalcet is effective in lowering serum Ca levels in PHPT, but is indicated solely in mild-asymptomatic PHPT meeting surgery criteria. Management of non-surgical mild-asymptomatic PHPT is still a debated issue.
Objective
To compare biochemical efficacy of Cinacalcet in controlling Ca levels in mild-asymptomatic PHPT patients fulfilling or not surgery criteria.
Design
This was a retrospective longitudinal cohort study.
Patients
43 sporadic PHPT patients (mean age 62.5 ± 10.6 years) with mild-asymptomatic disease, treated with Cinacalcet were included. Two categories were individualized: 23 patients with (category 1) and 20 patients without (category 2) surgery criteria. Median follow-up was 42 months.
Results
At the end of the initiation phase (3-month period with administration of 30 mg QD of Cinacalcet), the proportion of patients achieving normocalcemia was significantly greater in the group without indication to surgery (category 2) compared to the group fulfilling criteria for parathyroidectomy (category 1) (90 vs 56.5%; $P<0.001$). During the length of the study, normalization of serum Ca levels was observed in all enrolled subjects. Median (minimum and maximum) daily dose of Cinacalcet effective for obtaining and maintaining normocalcemia was 60 (30, 120) and 30 (30, 45) mg in category 1 and 2 respectively. Mean time of Ca normalization was significantly lower in category 2 rather than category 1 (3.1 vs 4.2 months; $P<0.001$). Mean serum Ca levels were significantly lower in patients without surgery indication (category 2) rather than subjects fulfilling surgical criteria (category 1) at 6, 12, and 36 months.
Conclusions
Cinacalcet is more effective in controlling serum calcium levels in non-surgical cases of mild-asymptomatic PHPT. Cinacalcet treatment should be considered in mild-asymptomatic PHPT, independently from the presence of surgery criteria.

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P129

Cardio-metabolic phenotyping of patients with familiar hypocalciuric hypercalcemia

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Introduction
Heterozygous inactivating mutations of the calcium sensing receptor (*CaSR*) gene cause mild alterations in calcium metabolism (familiar hypocalciuric hypercalcemia (FHH)). However, in addition to the parathyroid gland CaSR expression was recently identified in the myocardium and many other endocrine cells including pancreatic islet cells, entero-endocine cells and adipose tissue. So far, it is unknown whether FHH is associated with cardio-metabolic alterations that might be of clinical significance.
Methods
In eight FHH patients and nine controls matched for major anthropometric characteristics (45 ± 6 years; BMI 29.5 ± 2 kg/m^2), ectopic lipid deposition and heart function were investigated using magnetic resonance spectroscopy and imaging. Oral glucose tolerance test derived indices for insulin-sensitivity and -secretion, and endocrine responses to systemic calcium stimulation were studied.
Results
Insulin sensitivity (CLIX 4.5 ± 0.6 vs 4.3 ± 0.4 mg/kg per min; OGIS 399 ± 31 vs 419 ± 17 ml/(min$\times$m^2), basal (insulin secretion rate 266 ± 33 vs 218 ± 25 pmol/min) and glucose stimulated β-cell function (IGI: 140 ± 48 vs 118 ± 21 pmol/mmol and adaptation index 180.2 ± 12.2 vs 176.2 ± 17.4) as well as calcium stimulated insulin secretion were comparable between FHH and controls respectively. Also ectopic lipid accumulation in the liver (13.7 ± 15.4 vs $8.3\pm9.1\%$) and the myocardium (0.39 ± 0.3 vs $0.32\pm0.1\%$) as well as systolic (ejection fraction 71.5 ± 8 vs $72.8\pm8\%$ and cardiac index 2.35 ± 0.4 vs 2.35 ± 0.5 ml/min per m^2) and diastolic (E:A ratio 1.4 ± 0.6 vs 1.3 ± 0.7) myocardial function were not different between the groups.
Conclusion
Despite comprehensive cardio-metabolic phenotyping no clinically relevant alterations in myocardial function, lipid distribution, or glucose metabolism were observed. Thus, patients can be reassured that FHH reflects a laboratory finding with no need for intense medical surveillance.

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The relationship between microvascular complications and vitamin D deficiency in type 2 diabetes mellitus microvascular complications and vitamin D deficiency

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Aim
Vitamin D deficiency is reported as a risk factor for the development of diabetes in several epidemiologic studies. In this study, we investigated the frequency of 25-OH vitamin D deficiency in type 2 diabetes and the relationship between 25-OH vitamin D deficiency and microvascular complications.
Materials and methods
Retrospectively, medical records of 557 type 2 diabetic patients admitted to the Endocrinology Outpatient Clinic in January–March period and 112 healthy

controls who were randomly selected among individuals admitted to the hospital for a check-up and had a laboratory result of 25-OH vitamin D level were screened. The level of 25-OH vitamin D in type 2 diabetes and the relationship between 25-OH vitamin D deficiency and microvascular complications are investigated.
Results
There was not statistically significant difference in terms of 25-OH vitamin D levels between diabetic and control group. No correlation between $HbA1_c$ and vitamin D levels was found. 25-OH vitamin D level was lower in diabetic patients with nephropathy. Also patients not using any medication and followed by only dietary suggestion, had nephropathy in higher frequency.
Conclusion
Vitamin D deficiency is more common in diabetic patients with nephropathy. Upon evaluation of the total microvascular complications, vitamin D level was also lower. Vitamin D deficiency is associated with microvascular complications of diabetic patients.
Key Words
Type 2 DM, 25-OH vitamin D, microvascular complications.
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Evaluation of biochemical cardiovascular risk factors, carotid intima media thickness, and arterial stiffness before and after surgery in patients with primary hyperparathyroidism

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Primary hyperparathyroidism is a condition related with cardiovascular mortality and morbidity. Aim of this study is to investigate whether there is a difference between healthy controls, hypercalcemic patients with surgical decision and normocalcemic primary hyperparathyroidism patients for parameters like metabolic cardiovascular risk factors, carotis intima media thickness and pulse wave velocity and if there is a difference at patients with surgical decision 6 months after surgery or if there is a difference in patients with medical follow-up in time.
Seventeen hypercalcemic, 16 normocalcemic primary hyperparathyroidism patients, and 15 healthy controls were included to the study. Patient group was evaluated at the beginning and 6th month.
At the beginning of the study carotis intima media thickness was found higher at primary hyperparathyroidism patient group (patient group: 597 ± 80 μm and control group: 529 ± 91 μm, $P = 0.020$). Likewise at the beginning pulse wave velocity was higher at hyperparathyroidism patient group than healthy control group (9.5 ± 1.8 vs 7.7 ± 0.8 m/s, $P = 0.000$). Although there is a significant decrease at hypercalcemic patients for carotis intima media thickness after 6th month of the surgery (601 ± 91 vs 541 ± 65 μm, $P = 0.006$), no difference occurred at normocalcemic patients at the end of the 6th month ($P = 0.686$). Again there is a significant decrease at hypercalcemic patients for pulse wave velocity after 6th month of the surgery (9.6 ± 1.8 vs 8.4 ± 1.5 m/s, $P = 0.000$), no difference occurred at normocalcemic patients at the end of the 6th month for pulse wave velocity (9.4 ± 1.9 vs 10.0 ± 1.9 m/s, $P = 0.196$).
This result shows the importance of cardiovascular risk evaluation while making decision for treatment of primary hyperthyroidism patients and the need for earlier judgment makings for effective treatment options like surgery.
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Genu valgum in primary hyperparathyroidism in children

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Background
Bony deformity due to primary hyperparathyroidism is a rare entity in children.
Methods
We describe two children who presented with genu valgum to the Endocrine Department. Ten children with primary hyperparathyroidism presenting with genu valgum have been reported in literature and have been reviewed by us.
Results
Biochemical investigations revealed parathyroid hormone dependent hypercalcemia despite a deficiency of vitamin D in both children. A single parathyroid adenoma was identified by ultrasonogram and Tc-99 m MIBI scan. Both children underwent resection of the solitary parathyroid lesion which was confirmed as adenoma by histopathological examination. All cases reported in literature had solitary parathyroid adenoma and had onset around puberty consistent with our observation that pubertal growth spurt is responsible for the occurence of genu valgum in children with previously undiagnosed primary hyperparathyrodism.
Conclusion
Genu valgum is one of the commonest skeletal deformity in children with primary hyperparathyroidism. Solitary parathyroid adenoma was identified in all reported cases. Pubertal growth spurt seems to contribute to the occurence of genu valgum in children with primary hyperparathyroidism.
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Interdisciplinary aspects of primary hyperparathyroidism: symptomatology in a series of 100 cases (single-centre experience)

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Introduction
Primary hyperparathyroidism (PHPT) is a common endocrine disorder. Beside renal and skeletal complications, it has a wide variety of nonspecific symptoms from other organs that may mimic other diseases and delay the diagnosis. Nowadays PHPT evolves to less-symptomatic.
Aim
The aim is to revise symptomatology profile of PHPT in a single region of Poland; and to help early PHPT diagnosis – encouraging interdisciplinary contact between medical professionals.
Methods
We analyzed retrospectively data of 100 patients with PHPT diagnosed in our centre during the past decade: 94 women and six men, aged averagely 57.1 years (s.d. 13.7 years). We evaluated biochemical conditions (hypocalcaemia, hypercalciuria, hypophosphatemia, and PTH level elevation) and clinical manifestations: renal, skeletal, cardiovascular, gastrointestinal, and asymptomatic.
Results
Renal symptoms were present in 55%, as isolated symptoms in 14%. In the course of unrecognized disease seven cases of lithotripsy, seven operative lithotomies, two nephrectomies were performed. Osteoporosis/osteopenia was present in 66 and 10% respectively, and in 35% as the only PHPT presentation. In 16% fragility fractures, in 10% brown tumors were present. Fifty-five percent of PHPT patients were hypertensive and 21% ischemic heart disease positive. Gastrointestinal symptoms were present in 52%, in three cases (5.8% of 52), pancreatitis was documented. The incidental diagnosis of PHPT in asymptomatic patients was held in 15%. Mean serum Ca was 2.87 mmol/l (s.d.: 0.36), mean urine Ca was 15.97 mEq/24 h (s.d. 7.89), mean serum iPTH was: 324.11 pg/ml (s.d. 425.21). The duration time from any symptom appearance to the diagnosis varied between immediate diagnosis (19%), 1–10 years (46%), and >10 years (35%).
Conclusion
PHPT is still diagnosed too late, usually after a long time of untreated symptomatic disease. There is a need of active PHPT search. Multidisciplinary cooperation between specialists on the diagnostic level brings hope to avoid late complications of unrecognized disease.
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Serum 25-hydroxyvitamin D deficiency in acute cerebral strokes' patients with and without carbohydrate metabolism disturbances in North-Eastern part of Poland

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Introduction
The pleiotropic effects of vitamin D extend to control many physiological and pathophysiological processes in the human body. One of them is involved in the protective process of the nerve cells during stroke as well as pathogenesis of type 2 diabetes. Serum 25-hydroxyvitamin D concentration <20 ng/ml indicating vitamin D deficiency which is common in Poland. The aim of this study was to estimate serum level of 25-hydroxyvitamin D in acute ischemic strokes' patients with and without carbohydrate metabolism disturbances in North-Eastern part of Poland.
Materials and methods
We examined 59 patients with acute ischemic cerebral stroke admitted to the Department of Neurology in 2011–2013: 36 with carbohydrate metabolism disturbances and 23 without diabetes and prediabetes. Subjects underwent clinical and anthropometric assessment and blood tests were taken for measurement of 25-hydroxyvitamin D, fasting glucose, creatinine, calcium, and phosphorus.
Results
The mean age of participants was 66.1 (range 42–82). The mean and S.D. of 25-hydroxyvitamin D in strokes' patient in entire group was very low 8.1 ± 6.8 ng/ml. Mean 25-hydroxyvitamin D concentration in patients with carbohydrate metabolism disturbances was also below recommended level: 8.6 ng/ml (S.D. 6.1). Patients without carbohydrate metabolism disturbances had also very low concentration of 25-hydroxyvitamin D, 7.2 ng/ml (S.D. 7.7). We did not observe a significant difference between concentration of 25-hydroxyvitamin D in studied groups ($P=0.43$). Moreover, 50% of the patients had calcium level below the range norm.
Conclusion
Patients with acute ischemic cerebral stroke, with and without carbohydrate metabolism disturbances, should have supplementation of vitamin D, in north-eastern part of Poland.

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Estimation of optimal serum levels of 25-hydroxyvitamin D in a cohort of HIV-infected patients

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Introduction
25-Hydroxyvitamin D (25(OH)D) deficiency is a growing healthcare problem in HIV-infected patients. Evidence suggests that an optimal level of 25(OH)D would avoid secondary hyperparathyroidism but its optimal serum concentration has not been defined in HIV-infection. The aim of our study was to identify the 25(OH)D serum concentration that correlates to i-PTH increase and describe the prevalence of hypovitaminosis D in a cohort of HIV-infected patients.
Methods/designs
Cross-sectional study in HIV-infected subjects residing in the healthcare area of our Hospital's area of reference located in Southern Spain. 25(OH)D status were defined as normal, deficiency or insufficiency according to criteria of EuroSIDA prospective study. Secondary hyperparathyroidism was defined if serum levels of i-PTH were ≥ 65 pg/ml in absence of other diseases related to calcium and/or vitamin D metabolism.
Results
101 HIV-infected individuals were evaluated. Mean serum concentrations of 25(OH)D and i-PTH were 30.5 ± 13.8 and 47.6 ± 19.2 pg/ml respectively. 43.6% of the cohort was classified as having normal levels of 25(OH)D, 37.6% as insufficiency and 18.8% as deficiency. 13.9% patients had secondary hyperparathyroidism. There was a negative correlation between 25(OH)D levels and serum concentration of i-PTH ($r=-0.28$; $P=0.005$). 93% of the cases with an increased level of i-PTH had serum levels of 25(OH)D ≤ 28.5 ng/ml. On the ROC curve, the best sensitivity and specificity values were obtained if an optimal cut-off point for serum 25(OH)D, 21.4 ng/ml was used (area under curve: 84% and 95% CI 75–94%).
Conclusions
From a biological point of view, our results suggest that the normal ranges for our HIV-infected population could correspond to 25(OH)D levels ≥ 28.5 ng/ml, with a 93% of sensitivity to detect secondary hyperparathyroidism. The knowledge of these results could help us to decide which patients could be supplemented with vitamin D.

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Functional parathyroid cyst: a rare cause of hypercalcemia

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Primary hyperparathyroidism (PHPT) is usually caused by single adenoma. Functional parathyroid cysts are a rare cause of PHPT. Parathyroid cysts can be subdivided into nonfunctional, without biochemical derangement, or functional, with elevated serum calcium accompanying clinical evidence of hyperparathyroidism. Parathyroid cysts are found in the neck and anterior mediastinum. Functional parathyroid cysts are not only secretary but larger cysts can lead to compression symptoms, including dysphagia, dyspnoea, cough, stridor, and hoarseness. Mediastinum parathyroid cysts are usually presented as asymptomatic and identified accidentally by a routine chest X-ray or computed tomography (CT). We present a case of a patient with a functional parathyroid cyst.
Case
A 66-year-old male patients referred to our department because of hypercalcemia and anterior mediastinal mass determined on thorax CT done because of pulmoner embolism suspicion. He had no symptom of hypercalcemia except history of nephrolithiasis. Biochemical test revealed hypercalcemia with total serum calcium 12.24 mg/dl (8.8–10.2), phosphorus 2.98 mg/dl (2.5–4.5), parathyroid hormone (PTH) 140.6 pg/ml (15–65), creatinine 0.84 mg/dl (0.7–1.2), vitamin D 11.4 mg/l, and 24 h urinary calcium excretion was 504 mg/day. Renal ultrasonography determined 7 mm renal stone in the left kidney. Bone mineral dansitometry revealed osteopenia with -1.8 *T*-score. Thorax CT scan revealed a 4.7×3.3 cm sized solid mass, located in anterior mediastinum. After initiating of adequate hidration and furosemide treatment for hypercalcemia, the patient referred to chest and chest surgery department because of the anterior mediastinal mass and pulmonary embolism detected on thorax CT. The surgery decision was made because of the CT mass appearance. After removal of the mass calcium and parathyroid levels were reduced to normal levels. Pathologic examination revealed the diagnosis of a parathyroid cystic.
Mediastinal parathyroid cyst is an uncommon cause for hypercalcemia. It is difficult to establish a preoperative definitive diagnosis.

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Effects of nutritional intervention program on vitamin D serum levels in adolecents

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Introduction
Vitamin D deficiency and insufficiency is highly prevalent even in young people. Vitamin D status has been linked to the BMI and insulin resistance.

Aim
Determine 25(OH)D concentrations in adolescents before and after nutritional intervention program (NIP) and its relationship to BMI and metabolic syndrome (MS).
Methods
We selected 256 secondary school students (127 males) aged between 12 and 16 years from Granada (Spain), who were followed-up throughout one school year. In September and May it was determined 25(OH)D, food consumption frequency and both anthropometric and biochemical profile. The NIP comprised a class on nutritional and lifestyle recommendations for adolescents to achieve adequate growth, limiting TV/computer use substituted by outdoor activity and physically active, every 15 days and daily breakfast in school composed of a diary product rich in vitamin D, fruit, cereals, nuts, and sandwich with protein content.
Results
Preintervention, 18.7% of adolescents present vitamin D deficiency, 7.4% present a several deficiency, and 38.2% present insufficiency. After the NIP, the prevalence of deficiency was reduced to 0.46% ($P<0.0001$) and insufficiency was reduced to 19.1% ($P<0.0001$). The NIP effects depends on the BMI ($P<0.006$), fat mass ($P<0.05$), consumption of linolenic acid ($P<0.03$), and plama cholesterol ($P<0.02$).
Conclusion
The NIP has a powerful effect on vitamin D status, correcting the deficiency and reducing significantly the prevalence of insufficiency.

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Acute pancreatitis as the presenting feature and metabolic encephalopathy during the course of newly diagnosed primary hyperparathyroidism

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Primary hyperparathyroidism is the most frequent cause of hypercalcemia in adults. Hypercalcemia due to primary hyperparathyroidism is generally mild-moderate. Severe hypercalcemia in these cases is rare. Coexistence of severe hypercalcemia and hypercalcemic encephalopathy is very unusual with a very limited number of reported cases.
A 50-year-old female presented to the Emergency Department with symptoms of nausea and severe abdominal pain. Her serum calcium level was 19.4 mg/dl (8.8–10.2 mg/dl) and PTH level was 73.4 (15–65 ng/dl) on presentation. Her serum amylase levels were also elevated. After her hospitalization she was treated with saline infusions and furosemide however her calcium level increased to 22.4 mg/dl. The calcium level was also refractory to s.c. calcitonin 200 mg twice a day for 3 days and zoledronic acid 4 mg. Ultrasonography of the neck revealed a $3.2\times2.7\times4.6$ cm mass suspicious for a pathological parathyroid gland or a thyroid nodule adjacent to the left thyroid lobe. Considering her general situation getting worse despite maximum medical treatment, she underwent an emergency parathyroidectomy and left thyroid lobectomy. Early after the operation, the patient's general condition deteriorated reaching a pre coma state. The cranial computed tomography at this point revealed periventricular ischemia compatible with metabolic encephalopathy.
During the follow-up, the calcium levels normalized eventually requiring oral active vitamin D and calcium supplementation. She no longer presented symptoms of encephalopathy. The pathology specimen was reported as being compatible with an atypical parathyroid adenoma.
Although mild-moderate hypercalcemia is frequent in primary hyperparathyroidism it should be noted that it can be severe and refractory to maximum medical treatment requiring emergency surgical intervention. In addition, not being one of the most frequent reasons, severe hypercalcemia due to primary hyperparathyroidism should be considered as an important cause of metabolic encephalopathy.

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Ghrelin may have a role in obesity pathogenesis in patients with vitamin D deficiency

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Aim
Several studies suggest a link between vitamin D and obesity. Vitamin D may play a role in obesity. Ghrelin is an orexigenic peptide which induces obesity by central and peripheral mechanisms. Administration of ghrelin promotes food intake and decreased fat utilisation in rodents. Ghrelin levels are decreased in obese individuals.The aim of this study was to evaluate the relationship between vitamin D status and ghrelin levels.
Methods
All subjects applying to our clinic between December 2011 and February 2012 for whom 25 OH vitamin D3 (25(OH)D) levels measured were enrolled to this cross-sectional study. Those with a history of any metabolic disorder and those of any form of medication effect on obesity and vitamin D status were excluded. Patients were classified into two groups based on levels of 25(OH)D as group 1 (25(OH)D <20 ng/ml, $n=65$, and group 2 (25(OH)D ≥20 ng/ml, $n=30$.
Results
A total of 95 patients mean aged 35.06 (range, 18–57) years were enrolled in the study. Age and sex were similar between groups ($P>0.05$). BMI and waist circumference were found significantly higher in patients with group 1 than group 2 ($P<0.01$). HDL-C levels were also lower in patients with group 1 than group 2 ($P=0.05$). Also ghrelin levels were significantly higher in patients with group 1 than group 2 ($P<0.05$). On the other hand a significant positive correlation was established between 25(OH)D and BMI, HDL-C (respectively $r=-0.262$, $P=0.01$ $r=0.253$, $P=0.03$). However, a similar correlation was not found for the other metabolic parameters.
Conclusion
Vitamin D deficiency effects the ghrelin levels and ghrelin might contribute to the pathogenesis of weight gain and obesity in vitamin D deficient individuals. Further prospective clinical studies are needed to establish the relationship between ghrelin and vitamin D to clarify the pathogenesis of human obesity.

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Prospective evaluation of endocrine complications in adults with X-linked hypophosphatemic rickets

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Objectives
X-linked hypophosphatemic Rickets (XLHR) is characterized by phosphate wasting and decreased production of 1,25OH-vitamin D, due, in most patients, to elevated FGF23 and PHEX mutation. In children, the disease has been extensively studied because of the devastating presentation of rickets, teeth abcesses, and growth retardation. In adults, however, metabolic complications, such as hyperparathyroidism or consequences on glucose and lipid metabolism of FGF23 excess, have never been prospectively investigated.

Patients
Consecutive patients (35 years (21–48), 14F/6M), affected with XLHR and PHEX mutation, have been investigated 3 months after stopping their treatment (phosphate supplements and vitamin D analogues).
Results
As expected, patients presented with low serum phosphate (0.58 mmol/l, 0.34–0.88), elevated urinary phosphate (24 mmol/24 h, 16–52) and unadapted FGF23 (108 RUI/l, 60–387). Parathyroid function was found normal in 19/20 patients (calcemia: 2.29 mmol/l, 2.10–2.44; PTH: 33 pg/ml, 17–74; 25-OHvitamin D: 25 ng/ml, 14–44; calcitriol 54 ng/ml, 28–120; calciuria: 2.67 mmol/24 h, 0.94–6.63). Parathyroid scintigraphies and renal ultrasounds were normal in these patients. One patient was diagnosed with hyperparathyroidism.
Eleven patients were overweight or obese (BMI 25.6 kg/m^2, 20.9–42.2); one patient met the criteria for glucose intolerance on OGTT; five patients had abnormal lipid profiles.
Conclusion
Long-term consequences of phosphate wasting and calcitriol insufficiency, as well as metabolic consequences of FGF23 excess need to be evaluated. Tertiary hyperparathyroidism or renal impairment are not frequent. However, XLHR patients appear at increased risk of metabolic syndrome. The respective contributions of FGF23 and decreased physical activity remain to be determined.

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Vitamin D deficiency prevalence before and after sleeve or bypass in morbid obesity

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Rationale
Patients with morbid obesity may have vitamin D deficiency and bariatric surgery may exacerbate it due to factors such as lack of dietary compliance, reduced intake, malabsorption, etc.
Objective
To study vitamin D deficiency prevalence in patients with morbid obesity before and after bariatric surgery and its relationship with other laboratory parameters.
Methods
A retrospective study of 88 morbidly obese patients before and 1 year after surgery (bypass or sleeve). We collected data about: age, sex, previous comorbidities, physical examination, impedance testing, and laboratory parameters (25-hydroxyvitamin D, iPTH, Ca, HbA1c, total cholesterol, LDL, HDL, triglycerides, uric acid, and leptin).
Results
The mean age of patients was 45.1 ± 10.01 years, 78.4% women. Weight before and after surgery: 139.37 ± 27.46 vs 89.5 ± 16.89 ($P < 0.05$). Mean weight lost in bypass and sleeve patients was: 51.8 ± 18.1 vs 52.7 ± 24.1 kg ($P < 0.05$). One year after surgery there were significant decreases in HbA1c, TC, LDL, triglycerides, uric acid, leptin, and HDL increase. Mean serum 25-OH vitamin D pre and post bypass and sleeve was: presurgery 21.2 ± 20.2 vs 17.7 ± 8.8 ng/ml (NS) and postoperatory 27.0 ± 2.06 vs 30.6 ± 21.8 (NS). Mean PTH levels (bypass and sleeve): presurgery 51.8 ± 15.6 vs 67.1 ± 47.1 (NS) and postsurgery 53.9 ± 28.6 vs 41.1 ± 10.2 (NS). Percentage of deficiency (minor than 20 ng/ml) for by pass (pre and postsurgery) was: 41.9 vs 32.3% ($P < 0.05$) and for sleeve 43.5 vs 26.1% ($P < 0.05$). Hyperparathyroidism prevalence pre and postsurgery was: bypass 66.2 vs 64.6% (NS) and sleeve 50 vs 27.3% (NS). Mean PTH decrease in by pass and sleeve was: 1.8 ± 28.1 vs 29.1 ng/ml ($P < 0.05$) and vitamin D increase 4.3 ± 21.4 vs 9.6 ± 14.1 (NS). Vitamin D levels negatively correlated with preoperative age and body fat percentage. Vitamin D levels postsurgery correlated negatively with age. Mean postsurgery vitamin D levels in patients with BMI major and minor than 30 were: 23.97 ± 16.2 vs 40.5 ± 32.3 ng/ml respectively (P 0.05). Mean postsurgery vitamin D increase correlated with 1 year BMI (r: −0.45; P 0.05).
Conclusions
Patients with morbid obesity have vitamin D deficiency in high percentage of cases preoperatively, which should lead us to measure 25-OH vitamin D levels routinely. After the surgical procedure, despite systematic supplementation, patients maintain a high percentage of vitamin D deficiency and elevated iPTH.

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P142

Vitamin D deficiency in Russian pregnant women and risk for gestational diabetes

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Introduction
Some, but not all, previously published studies suggest that low vitamin D status maybe associated with increased risk of gestational diabetes (GDM). We examined the association of plasma plasma 25-hydroxyvitamin D (25(OH)D) concentration with GDM risk and neonatal macrosomia.
Methods
143 women were recruited before 15 weeks of gestation and were followed-up until delivery. Maternal plasma 25(OH)D concentrations were measured at 8–14 weeks of gestation. Two-hour 75 g oral glucose tolerance test (OGTT) was performed between 24 and 28 weeks of gestation. GDM was diagnosed according to IADPSG criteria. The neonatal anthropometry was also measured.
Results
GDM was revealed in 19 women (13.3%). Mean 25(OH)D levels were 21.8 ± 8.5 and 21.9 ± 9.2 ng/ml ($P = 0.984$) and the prevalence rates for vitamin D deficiency (25(OH)D levels < 20 ng/ml) were 52.6 and 45.2% ($P = 0.625$) in women who developed GDM and in women without GDM respectively. Maternal 25(OH)D was unrelated to the results of OGTT or neonatal anthropometry. Only 19% of women reported the use of vitamin D supplements before the first prenatal visit and 57.4% of women had been taking it by the time of OGTT performance
Conclusion
Early pregnancy vitamin D deficiency was very common in the studied population of pregnant women. There was no association between maternal 25(OH)D and gestational diabetes.

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P143

Variety of vitamin D receptor gene polymorphisms and serum levels of vitamin D in patients with type 1 diabetes

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Currently relationship between the decrease in vitamin D (VD) levels and the formation of bone pathology has established. The presence of certain VD receptor (VDR) polymorphisms has been suggested to be associated with the serum VD. Therefore, the aim of study was to assess the association between VDR single nucleotide polymorphisms (SNPs) in type 1 diabetic patients and serum VD.
Materials and methods
We studied 66 type 1 diabetic (T1D) patients (28 men and 38 women; mean age 31.23 ± 8.41; duration of the disease 13.40 ± 7.41; and HbA1c 8.25 ± 0.95%). The research involved anthropometry of patients, general clinic examination. The following parameters were evaluated: levels of VD, C-terminal telopeptide (CTX), VDR genotyping analysis (VDR-FOKI, FokI (BseGI) and VDR-ApaI, ApaI).
Results
There was a substantial decrease in serum levels of VD in TID patients compared with the control (48.66 ± 6.13 vs 123.47 ± 15.49 nmol/l, $P < 0.001$). There were significant differences in the levels of VD in patients with VDR, ApaI SNPs: wild homozygotes 37.5 ± 8.12, in heterozygotes 44.2 ± 12.35, in mutant homozygotes 71.29 ± 16.36 nmol/l, $P < 0.001$. Similar data were obtained among carriers individuals with VDR-FokI SNPs (27.32 ± 4.89 vs 53.135 ± 4.67 vs 58.2 ± 7.7 nmol/l, $P < 0.001$).
Conclusion
The results of the study reflect a significant decrease serum VD in patients with TID and VDR gene polymorphism's influence on these processes to need further study.

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P144

Recurrent post-surgical hyperparathyroidism: think of *CYP 24A1* mutations!

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CYP24A1 gene encodes 24-hydroxylase that inactivates 1-25-OHvitaminD. Mutations induce infantile hypercalcemia, with high 1-25-OHvitaminD, contrasting with low PTH levels. Adult phenotypes are not well known yet. We report two cases of post-surgical persistent hypercalcemia, related to *CYP24A1* mutations. Two unrelated patients, a 40-year-old female (#1) and 54-year old male (#2), were referred for nephrolithiasis, enthesis and hypertension in both, associated to nephrocalcinosis in #1, osteopenia in #2. Before surgery, their respective biological characteristics were as follows: (#1/#2) calcemia: 139/111 mg/l (*n*: 85–105); phosphatemia: 28/27 mg/l (*n*: 25–45); PTH: 92/22 pg/ml (*n*: 15–68); 25-OHvitaminD: 38/26 ng/ml (*n*: 30–80); 1–25-OHvitaminD: 120/56 pg/ml (*n*: 18–70); creatinine: 12/15 mg/l (*n*: 7–10); calciuria: 434/400 mg/24 h (*n*: 60–300). In #1, cervical echography and Tc-MIBI-scintigraphy were negative but tomodensitometry showed a left inferior parathyroid hypertrophy. Surgery did not enable to find the pathological gland leading to subtotal parathyroïdectomy, left thyroid lobo-isthmectomy and thymectomy. Pathological examination showed hyperplasia of the two superior parathyroid glands and three papillary thyroid microcarcinomas (PTC). In #2, cervical echography, scintigraphy and tomodensitometry showed a 10 mm right parathyroid lesion corresponding to an adenoma after surgery. Calcium levels remained high post-surgery in both with a partial efficacy of cinacalcet. A compound heterozygote mutation of *CYP24A1* (#1: p.Cys380Arg/p.Leu409Ser; #2: c.13DUPc.1/27GA in exons 7–8) were identified. Conclusion i). *CYP24A1* phenotype can evolve with time from hypercalcemia with low PTH to a biological profile suggesting hyperparathyroidism. ii). Whatever morphological investigations, surgery is ineffective. iii). An increased frequency of PTC has been reported. iv). Increased 1-25OH and 25OHvitaminD without supplementation should suggest the diagnosis, which can be confirmed by investigating CYP24A1 gene mutation. 5. Sun and vitaminD eviction, hyperhydratation ± cinacalcet or ketokonazole are recommended.

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P145

The association between vitamin D deficiency and metabolic parameters in pediatric obesity is influenced by what surrogate index of sunlight exposure is used

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Introduction
The association between vitamin D (25(OH)D) levels and metabolic parameters is not confirmed in some population studies. 25(OH)D concentration in blood is influenced by seasons and this covariate may explain some discordant results. The first aim of our study was to evaluate the prevalence of 25(OH)D deficiency in a population of obesity children (2–18 years) living in the North of Italy (latitude, 45°27′*n*) with respect to the season. The second aim was to decipher whether the association between 25(OH)D levels and metabolic parameters is influenced by different indexes of sunlight power as covariates.
Methods
Clinical and metabolic evaluations including an OGTT were performed in 640 obese children and adolescents (BMI IOTF classification). 25(OH)D levels were stratified according to classical cut-off ranges (deficiency: <20 ng/ml; hypovitaminosis: 20–30 ng/ml, and normal values: ≥ 30 ng/ml) and also divided in quartiles. Sunlight power was evaluated as season, month radiation, or u.v. index.
Results
291 subjects (45.5%) had 25(OH)D deficiency. 25(OH)D deficiency showed a seasonal trend ($\chi^2=113.4$, $P<0.0001$) with a higher prevalence in autumn and winter. The correction for month radiation or u.v. index showed more significant results than that for seasonality. Levels of total cholesterol ($P<0.001$), triglycerides ($P<0.001$), insulin during OGTT ($P<0.01$) were negatively predicted by 25(OH)D quartiles independently by BMI–SDS, puberty, and month radiation. The correction for the u.v. index strengthened the significance of previous results, and showed other correlations with blood pressure ($P<0.02$), HOMA index ($P<0.01$), and insulin levels at fasting ($P<0.01$), at 60′ ($P<0.04$) and 90′ min ($P<0.002$).
Conclusions
The prevalence of 25(OH)D deficiency is high in the obese pediatric population and has a seasonal trend. Since sunlight exposure has a role, studies on vitamin D should use correction for indexes of sunlight exposure. Some indexes seem more accurate than others and these aspects could explain some discordant results in literature.

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P146

Three patients with idiopathic hypoparatiroidism presented with different clinical manifestations

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Aim
Patients with hypoparatiroidism may admit to hospitals with different symptoms.In this report we presented 3 case of hypoparatiroidism with congestive heart failure,epilepsy and muscle pain.
Case 1
31-year-old male admitted to hospital with dyspnea on lying down and evaluation revealed pericardial and pleural effusion. The patient was hospitalized to cardiology clinic with a prediagnosis of decompansated heart failure. In echocardiography ejection fraction was 17%, in laboratory tests calcium, phosphor and intact PTH (iPTH) values were 2.9 mg/dl (8.5–10.0), 6 mg/dl and <3 pg/ml respectively. He had no thyroidectomy or parathyroidectomy history. The patient was performed a cataract surgery 5 years ago. Patient was treated with calcium and calcitriol. After normalization of calcium patient's ejection fraction rate was 35% 10 days later and 50% 3 months later.
Case 2
A patient with a history of epilepsy for 5 years admitted to neurology policlinic and routine laboratory evaluation revealed hypocalcemia (4.9 mg/dl) and patient referred to endocrinology policlinic in terms of hypocalcemia causes. In laboratory tests phosphor was 6 mg/dl and iPTH was <3 pg/ml. In medical history he has tingling in his hands and feet for 4–5 years and after an epileptic seizure he started to use anti epileptic drugs. Patient was treated with calcium and calcitriol. After normalizing calcium levels anti-epileptic drugs were ceased by neurology. He didn't suffer epileptic seizures on his follow-up.
Case 3
33-year-old male admitted to hospital with complaints of spasm in his hands and feet, hypocalcemia detected and patient referred to endocrinology policlinic. Laboratory investigation were as follow; calcium 6.3 mg/dl, phosphor 6 mg/dl, iPTH <3 pg/ml, and creatinine kinase 6134 U/l (20–200). Patient was treated with calcium and calcitriol. After normalizing calcium levels creatinine kinase levels and symptoms improved.
Conclusion
Most common finding of hypocalcemia is tetany.Hypocalcemia impair the balance between stimulus and contraction and causes various findings such as congestive heart failure. Increased creatinine kinase levels is reported in hypocalcemia. It should be keep in mind that epilepsy may be a symptom of hypocalcemia.

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P147

Hypoparathyroidism and celiac disease a rare autoimmune disease combination

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Case
A 30-year-old man with hypoparathyroidism has been treated with calcitriol and calcium for 2 years, admitted hospital with persisting diarrhea. An endoscopic operation is planned. But when he was waiting for this examination as outpatient condition, he had a convulsion and had been taken in hospital by parents. Initial laboratory analyses revealed that he was hypocalcemic (total calcium of 6 mg/dl) and parathormone (PTH) 8 pg/ml, phosphorus 5.7 mg/dl, and magnesium 2 mg/dl. He was treated with i.v. calcium gluconate urgently. Then treated with oral calcium gluconate and calcitriol with a stepwise increase in the dosage. An upper gastrointestinal system endoscopy has taken. Diagnosis of gluten-sensitive or celiac disease was suggested at endoscopy, due to flat mucosa and confirmed by histological findings in duodenal biopsy including absent villi, crypt hyperplasia and lymphocytic infiltration in the epithelium. Serologic examination confirmed the diagnosis. Then he was placed on gluten-free diets, which rapidly lead to the normalization of his bowel habits and improved his metabolic parameters. The needed drug dosage decreased.
Conclusion
Hypoparathyroidism is an uncommon endocrine-deficiency disease characterized by low serum calcium levels, elevated serum phosphorus levels, and absent or inappropriately low levels of PTH in the circulation. After postoperative hypoparathyroidism, autoimmune hypoparathyroidism is the next most common form of hypoparathyroidism in adults. Patients with hypoparathyroidism most often present with paresthesia, cramps, or tetany, but the disorder also may manifest acutely with seizures, bronchospasm, laryngospasm, or cardiac rhythm disturbances. Autoimmune hypoparathyroidism may be isolated or part of an autoimmune polyglandular syndrome. Celiac disease and autoimmune hypoparathyroidism togetherness is a very rare condition but the possibility of celiac disease should be considered in patients with hypoparathyroidism that seems unduly difficult to treat.

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P148

Paternal isodisomy is a frequent cause of pseudohypoparathyroidism 1-b

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Patients affected by pseudohypoparathyroidism type 1b (PHP-1b) develop resistance to PTH leading to hypocalcemia and hyperphosphoremia, which is often associated with resistance to TSH. PHP-Ib is associated with methylation changes at one or several differentially methylated regions (DMRs) within the GNAS complex locus, located at 20q13.2–13.3. This locus gives rise to several different transcripts (NESP55, XL, A/B), with varying patterns of expression depending on the parental allele and the methylation status of the specific exon 1 promoters.
PHP-Ib may follow an autosomal dominant pattern of maternal inheritance associated with deletion in *STX16* or it can arise sporadically.
Epigenetic changes observed in genomic DNAs from sporadic PHP-Ib mimic the paternal-specific methylation pattern without maternal epigenetic marks.
Uniparental disomy (UPD) is a condition in which a chromosomally disomic individual inherited both copies of a chromosome from one parent only. Thus, paternal UPD20 is a plausible cause of PHP-1b.
We screened a cohort of 57 unrelated patients presenting with sporadic PHP-1b and broad *GNAS* epigenetic changes to evaluate the frequency of patUPD20.
Comparative genomic hybridization (CGH) combined with SNP-array (Agilent 4×180K sureprint G3 Cancer) was used to identify copy number variant and loss of heterozygosity (LOH). Single nucleotide polymorphisms or short tandem repeats were studied along chromosome 20 in the proband and compared to his two parents to confirm LOH.
Because GCH arrays required high quality DNA only 20 samples were tested.
We found four patients (20%) with patUPD20: two patients with complete patUPD, one patient with patUPD of the long arm of chromosome 20 and one patient with a large interstitial UPD20 including *GNAS* locus. We also detailed the phenotype and the DNA methylation pattern of these patients.
This study suggests that patUPD20 is a frequent cause of PHP-1b that should be tested in the evaluation of patients with sporadic PHP-1b.

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P149

Frequency of vitamin D deficiency in pregnant diabetics

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Objective
Gestational diabetes mellitus (GDM) is defined as glucose intolerance that is first diagnosed during pregnancy resulting from pregnancy associated insulin resistance and impaired insulin secretion. We aimed to investigate the frequency of vitamin D deficiency and its relation with glucose parameters and the incidence of gestational diabetes.
Materials and methods
Gestational diabetes was diagnosed with 75 g oral glucose tolerance test. 32 pregnant women diagnosed with GDM. Serum, 25(OH)D, calcium (Ca), phosphorus (P), TSH, and HbA1c, were also measured. Vitamin D status was classified as deficiency at $\leq$20 ng/ml for serum 25(OH)D concentrations.
Results
The mean ages were 32.06$\pm$6.22 (20–43) years. The mean vitamin D level was 19.36$\pm$12.07 ng/ml. The mean calcium level was 9.06$\pm$0.32. The mean fasting glucose level was 95.75$\pm$14.74. The mean HbA1c level was 5.83$\pm$1.29. The mean TSH level was 1.95$\pm$0.95. There was no significant association between vitamin D levels and fasting glucose, TSH, and HbA1c.
Conclusion
Our study provides data indicating that maternal vitamin D deficiency (serum 25(OH)D $<$20 ng/ml) is prevalent among our pregnant population. However we did not find significant association of low levels of serum 25(OH)D with elevated risk for GDM even after adjustment for conventional risk factors for diabetes. The association of maternal vitamin D status with the markers of glucose metabolism in pregnancy needs prospective studies.

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P150

Vitamin D seasonal variation of elderly people in Konya Residantal Care

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Introduction
Many factors influence intensity and duration of exposure to ultraviolet, including geographic location, season, dietary intake, atmospheric conditions and the daily sunlight exposure. Study was performed to determine prevelance of hypovitaminosis in housebound elderly.
Design
41 people (22 men and 19 women) living in Konya Residantal Care (RC) were taken. Serum 25-OH vitamin D (VD) measured in winter and in summer. Results were evaluated between each other and 20 elder persons (ten women and ten men) who had the similar demographic conditions, healty and live outside the RC.
Results
RC people mean age were 74.75$\pm$3.90, in control groups (CG) were 74.75$\pm$3.90. Mean VD level in summer, in winter were 20.36$\pm$6.54–19.29$\pm$6.00 ng/ml for men, 19.58$\pm$6.93–18.29$\pm$4.69 for women: respectively in RC group. Mean VD level in summer, in winter were 24.79$\pm$6.59, 20.94$\pm$5.29 for men, 25.30$\pm$6.77–20. 73$\pm$6.50 for women in control group. There was no difference in mean values between RC people and CG, in the summer and winter period. In RC men mean VD levels, there was no difference between CG men in summer (P=0.119) and in winter (P=0.269). In RC women mean VD levels there was significant difference (P=0.008) in summer to control women, in winter there was no difference (P=0.146). physical activity (PA) evaluated in RC people as enough or not, in winter and summer there was no significant difference between on sufficient PA acording to insufficient PA (winter P=0.237 and summer P=0.173). The avarage VD intake were found much lower than the recommended in RC and control group.

Conclusion
Increasing incidence of hipovitaminose in persons who live in RC and CG in winter period was due to Inadequate intake insufficiant sunlight exposure and physical inactivity. For this especially in RC people PA must be increased besides intake of vitamin D and calcium suplement to prevent the risk of falling and fracture.

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P151

Oncogenic osteomalasia: a rare case due to lipoma

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Introduction
Oncogenic osteomalasia is a rare paraneoplastic syndrome in which a tumor produces fibroblast growth factor 23 which leads to increased urinary phosphate excretion resulting in hypophosphatemia. It is frequently associated with mesenchymal tumors of bone and soft tissues. We report a case of oncogenic osteomalasia due to lipoma.
Case report
A 38-year-old female patient with a 6-year history of left hip pain which progressively worsened over years. Owing to the pain and muscle weakness especially in her lower extremities she gradually became unable to walk. When she was admitted to our clinic she had severe diffuse muscle pain, she was bed-ridden, she was unable to walk. Physical examination revealed 2 cm subcutaneous, dome-shaped, smooth, mobile noduler lesion on abdomen below umblicus. Laboratory testing was remarkable for low serum phosphorus, increased urinary phosphate excretion, elevated serum FGF23 level, normal calcitriol which was consistent with oncogenic osteomalasia. Excisional biopsy was performed for lesions described on abdomen. Pathological examination of lesion on abdomen reported as lipoma. Phosphate levels gradually increased and returned to normal 5 days after excision of lesions. Muscle weakness gradually improved on folllow-up visits, she became able to walk without support. She is being followed-up in our clinic with normal phospfate levels and she is clinically well.
Conclusion
Oncogenic osteomalasia is an important cause of hypophosphatemia which may be debilitating for the patient. Our case is a very rare case of oncogenic osteomalasia due to lipoma.

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P152

The effect of VDR polymorphisms on serum testosterone level in aging men population

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The aim of this study was to determine whether polymorphisms (TaqI, ApaI, BsmI, and FokI) of the vitamin D receptor (VDR) show a correlation with the serum level of the testosterone in the aging men population.
A group of 224 men aged 65–90 years, randomly selected from the group of 5695 persons included in the PolSenior project was studied. We established genotype prevalence of the VDR gene polymorphisms (TaqI, rs10735810; ApaI, rs1544410; BsmI, rs7975232; FokI, and rs731236) and testosterone serum concentration levels. Polymorphisms were divided into two models: protective (Taq, TT genotype; Apa, aa genotype; Bsm, genotype BB; and Fok, genotype FF) and risk (Taq, tt genotype; Apa, AA genotype; Bsm, genotype bb; and Fok, genotype ff). The cumulative effect of these two models on the concentration of testosterone were calculated.
Risk model of the polymorphism Fok shows significantly higher serum levels of the testosterone than the protective model ($P=0.0436$).
Although the carriers of the protective model of Apa, Taq and Bsm polymorphisms have a higher serum testosterone level, it doesn't reach statistical significance ($P=0.5568$, $P=0.6327$, and $P=0.0653$).
Analysis of the combined effect of all models of polymorphisms indicates that the protective model is associated with higher levels of testosterone, but it doesn't reach statistical significance ($P=0.7908$).
Project requires further research with a larger group of patients.

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P153

The change in paratyroid hormone level by posture in primary hyperparathyroidism

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Introduction
Major factor that modulates the PTH secretion is serum Ca level. Paratyhyroid gland also receives direct autonomic innervation. To date, measurement of several hormones such as cortisol,prolactin, renin and aldosteron were found to be affected by changing the posture from recumbent to the upright position. In the present study, we aimed to investigate postural change of PTH in normal individuals and patients with primary hyperparathyroidism (PHPT).
Methods and results
23 patients with PHPT and nine healthy controls were enrolled. Blood samples were taken from all indivuduals after 12 h of fasting. Following replacement of an i.v. catheter, the patients were requested to rest in bed in recumbent position but not sleeping for an hour and blood samples were obtained for PTH and Ca measurements at the 45th and 60th min of resting. Afterwards, the patients changed the posture to the upright position and stood up for an hour and again blood samples were obtained at the 45th and 60th min of standing. Pulses and blood pressures of all individuals were recorded in both postures. In the group of patients with PHPT, mean serum PTH was measured as 75.36 pg/ml higher during upright position compared to recumbent position and the difference was statistically significant. Mean serum Ca was also significantly higher in upright position. In the control group mean serum PTH was measured only 3.09 pg/ml higher during the upright postion compared to recumbent position and the difference didn't reach statistical significance. However mean serum Ca level was 0.46 mg/dl higher during the upright postion compared to the recumbent which resulted in a statistically significant difference.
Conclusion
It was reported that total calcium measurement increases in upright posture which should normally decrease the measured PTH level. However PTH secretion is autonomic in PHPT and increased in upright position regardless of serum Ca level.

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P154

Postprandial blood glucose and fetuin-A are independently linked to the coronary calcification progression in patients with type 2 diabetes

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Introduction
Coronary calcification (quantified as Agatston's calcium score (CS) and measured with a CT-based method) has been shown to predict coronary atherosclerotic burden and mortality in type 2 diabetics (T2D). Compared to a single measurement, the progression of CS in time better reflects the effects of cardiovascular risk factors that have not yet been fully elucidated.
Methods
We measured calcium score (CS) (Agatston's method, 64-slice MDCT) in 45 T2D without renal disease (23 males, average $\pm$ SD for duration of diabetes 10 ± 8 years, BMI 31 ± 5) initially and after 18 months. We also measured HbA1c, femoral neck mineral bone density, blood pressure, serum calcium, phosphate, 25-OHD, intact PTH, fetuin-A, hsCRP, alkaline phosphatase, albumin, homocysteine, triglicerides, total, LDL and HDL cholesterol. Patients self-monitored preprandial and postprandial blood glucose (BG) (at least one day per week). We calculated Spearman's correlation coefficients (for absolute and relative change in CS) and performed multiple linear regression (CS were ln-transformed for non-normality).

Results
Median (IQR) of CS at baseline was 63 (6-384), after 18 months 100 (13-532). Mean (±SD) preprandial BG was 7.84±0.85 mmol/l, postprandial BG 9.50±1.62, HbA1c 7.5±0.9%. Mean fetuin-A (for both measurements) was 26.8±5.0 ng/ml. We found significant correlations between absolute and relative change in CS and fetuin-A and relative change in CS (P 0.05). For other bivariate pairs P was >0.05. In multiple regression, based on postprandial BG and fetuin-A, both remained significant (R for model 0.497, F 5.941, P 0.006).
Conclusions
Postprandial BG and fetuin-A seem to be independently related to coronary calcification progression in T2D. Higher postprandial BG levels contribute to calcification progression. Higher fetuin-A appears to be protective in our patients, although further research is warranted.

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P155

Denosumab increases bone mineral density in primary hyperparathyroidism treated with Cinacalcet

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Cinacalcet decreases and normalizes serum calcium levels across a broad severity range of primary hyperparathyroidism (PHPT), slightly reduces parathyroid hormone levels which generally remains elevated, whereas it has no effect on bone mineral density (BMD). Therefore, when administering Cinacalcet to a patient with PHPT, concomitant treatment with an anti-catabolic drug should be considered.
An open-labeled, prospective trial was conducted in 30 patients with PHPT with Cinacalcet treatment (contraindications to surgery: comorbidities, high surgical risk and age, clinical judgment of inappropriate parathyroid surgery (PTx): negative parathyroid imaging, persistent or relapsing PHPT after PTx- and refusal of PTx), to determine whether denosumab, maintains or improves BMD in patients with PHPT after a year of treatment.
PHPT patients with low BMD were treated with Cinacalcet (Mimpara, Amgen; titrated dose), 25-OH vitamin D (Hidroferol, Faes) and denosumab (Prolia, Amgen) 60 mg s.c. injections given every 6 months. Serum calcium, phosphorous PTH, and bone turnover markers were evaluates every 3 months. BMD was measured at the lumbar spine (LS) and total femur (TF) by dual-energy X-ray absorptiometry baseline and after 12 months of treatment.
The treatment normalized calcium, phosphorous, and 25(OH)D serum levels and urinary calcium excretion. Bone turnover markers remained suppressed for the duration of the trial. The treatment was also associated with a significant increase after 12 months in vs baseline in LS BMD: 3.7% (P: 0.0001) and in TF BMD: 1.854% (P: 0.03).
Denosumab associated to Cinacalcet is an excellent therapeutic option to normalize serum calcium and to treat the metabolic bone-disease in patients with PHPT who do not meet criteria for surgical treatment.

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P156

Vitamin D in men with metabolic syndrome with low or normal testosterone levels

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Introduction
The classical role on calcium homeostasis played by vitamin D is well documented. Lately vitamin D is linked to a variety of chronic diseases related to ageing, diabetes, and cardiovascular diseases. However, the pathophysiological roles of vitamin D in such cases are unclear.
Aim
To clarify the relation of metabolic syndrome (MS), testosterone levels, and vitamin D status in men.
Patients and methods
99 male patients of Endocrinology Clinic in University hospital 'Alexandrovska' with MS were additionally evaluated for their testosterone level and vitamin D status. Of them 65 had MS and they were divided according to their morning total testosterone (TT) level (cutoff 10.4 nmol/l) into two groups: MS-low testosterone ($n=21$) and MS-normal testosterone ($n=44$). The control group consisted of 34 age-matched men without MS and with normal TT. Vitamin D levels were measured using electrochemiluminiscence immunoassay.
Results
MS men were at mean age (±s.d.)=50.4±9.6 years; BMI=33.3±7.7 kg/m^2; and TT=13.6±5.4 nmol/l. The control group was at age=51.5±6.4 years (NS); BMI=25.7±2.4 kg/m^2 ($P<0.001$); and TT=17.9±5.6 nmol/l ($P<0.001$). The levels of vitamin D were higher in the control group – 27.9±12.0 ng/ml compared to the MS one – 16.2±9.1 ng/ml ($P<0.001$). Vitamin D sufficiency was found in 73.5% of the patients in the control group and only in 31% of the men with MS. Nobody in the control group was found to have vitamin D deficiency but 28% of the MS group had it and additionally 41% had insufficient levels of vitamin D. Correlation between vitamin D and TT level was not found.
Conclusion
Vitamin D status is correlated only to the persistance of the MS. The role of vitamin D and testosterone levels and their relation to one another and to the MS has to be clarified in future studies.

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P157

Is parathyroid hormone venous sampling useful? Correlation of parathyroid hormone selective venous sampling and histopathological results in patients who underwent parathyroidectomy between 2006 and 2013

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Patients with primary hyperparathyroidism (PHPT) undergo parathyroid ultrasound, Tc-99m sestamibi scan or MRI to localize hyperfunctioning parathyroid gland(s). When scans are negative or discordant we perform parathyroid hormone selective venous sampling (PTHSVS).
We report the results of 18 patients (four males, 14 females, average age 58.7) with PHPT, who underwent PTHSVS followed by either focused parathyroidectomy (FP) or bilateral neck exploration (BNE) in years 2006–2013.
All patients had both parathyroid ultrasound and Tc-99m sestamibi scans. Parathyroid ultrasound showed lateralisation in 27.8% (16.67% possible and 11.1% confident) and Tc-99m sestamibi showed lateralisation in 33.3% (27.8% possible and 5.56% confident). In 11.1% of patients lateralisation was present on both scans but results were discordant.
On average during the PTHSVS procedure samples for PTH levels were obtained from 10.78 sites. All procedures were successful.
PTHSVS showed lateralisation in 12 patients (66.7%). Following the results of PTHSVS ten patients underwent FP, two had BNE. Histopathological results confirmed nine adenomas (75% true positive). In remaining three cases (25% false positive) there was one confirmed hyperplasia and one positive PTHSVS is thought likely to contain a spurious PTH result.
The average ratio between the site of highest PTH level and level of PTH in inferior vena cava was 7.37 (2.61–19.38) in patients with lateralisation.
In six patients with no lateralisation on PTHSVS, three had BNE, and three FP. Histopathological report in five patients confirmed existence of parathyroid adenoma (83.3% false negative). One patient had hyperplasia (16.7% true negative).
Seven out of ten patients who had FP were cured during first operation. Three patients required reoperation, one of them was not cured due to anatomical localization of the adenoma.
Our report suggests that PTHSVS is a helpful diagnostic adjunct in localization of hyperfunctioning parathyroid gland(s). Positive PTHSVS increases the surgeon's confidence in choosing a less invasive procedure.

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P158

Evaluation of the relationship between vitamin D concentration and selected clinical and biochemical features in women with polycystic ovary syndrome

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Introduction
Vitamin D deficiency (25OHD) is common in women with polycystic ovary syndrome (PCOS). 67–85% of female patients with PCOS have low concentration level of 25OHD (<20 ng/ml). It is believed that low concentration levels of 25OHD may exacerbate the symptoms of PCOS.
Aim
The aim of the study was to evaluate the concentration of 25OHD in women diagnosed with PCOS and the analysis of the relationship between 25OHD concentration and such features as: BMI, insulin resistance (HOMA-IR >1.0), menstrual disorders, clinical, and biochemical hyperandrogenism.
Material and methods
Clinical and biochemical data of 51 women with PCOS (mean age 25.4 years) were analysed. PCOS was diagnosed according to the Rotterdam criteria (2003). In the tested group, 46 (90.2%) patients with PCOS had menstrual disorders, 44 (86.3%) had hirsutism, 43 (84.3%) insulin resistance, and 14 (27.4%) suffered from obesity. The analysis focused on the dependence between 25OHD concentration and BMI, HOMA-IR >1.0, menstrual disorders, hirsutism, testosterone, androstendione, and DHEA-S. In statistical analysis a Pearson's correlation coefficient, Spearman's rank correlation coefficient as well as χ^2 test, Fisher's exact test and Mann–Whitney U test were used as appropriate. A P value <0.05 was considered to be significant.
Results
25OHD concentration ranged from 4.1 to 73.3 ng/ml (mean concentration of 29.25 ng/ml). 15 patients (29.4%) had 25OHD concentration level below 20 ng/ml. There was found a statistically significant negative correlation between 25OHD concentration and concentration of serum testosterone ($P=0.01$). The negative correlation between 25OHD concentration and the incidence of obesity, HOMA-IR >1.0, hirsutism, menstrual disorders, and serum androstendione level and also DHEA-S was not significant statistically.
Conclusions
i) The percentage of female patients with PCOS and 25OHD deficiency is significantly lower than in most previously published studies.
ii) In women with PCOS, the low concentration level of 25OHD is associated in a statistically significant way with higher serum testosterone level.

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P159

Hypercalcaemia presenting as hyperemesis gravidarum in a pregnant patient

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Background
Primary hyperparathyroidism during pregnancy is rare, and may present with symptoms non-specific to hypercalcaemia.
Case
A 35 years old 12/40 weeks pregnant lady presented to accident and emergency department with 6 weeks history of nausea and vomiting. On admission she felt anxious with ongoing nausea and numbness all over the body. She was a mother 2-year-old with no significant past medical history. Her medication on admission were; folic acid 5 mg once daily, metochropromide 10 mg three times daily when required, and pregnacare ones tablets once a day. Her blood test showed Na^+ 137 mmol/l, K 3.4 mmol/l, urea 2.4 mmol/l, creatinine 61 μmol/l, ALP 79 μ/l, ALT 32 μ/l, albumin 36 g/l, bilirubin 10 μmol/l, corrected Ca^{2+} 3.50 mmol/l, phosphate 0.71 mmol/l, magnesium 0.70 mmol/l, parathyroid hormone 15.2 pmol/l, and TSH 0.50 μ/free T_4 9.5 pmol/l. 24 urinary calcium was elevated at 17.5 mmol/24 h. Ultrasound parathyroid revealed 9 mm left lower lobe parathyroid adenoma.She was started on i.v. fluids for 72 h and her calcium remained high at 3.05 mmol/l but she generally felt well. She was discharged home and referred to surgical team for review and consideration of surgery but she was readmitted 1 week later with general malaise and ongoing nausea and vomiting. She had parathyroidectomy at 14/40 gestation weeks with normalisation of calcium.
Discussion
Primary hyperparathyroidism may be associated with adverse outcome in the fetus and neonate. Adequate hydration and correction of electrolyte abnormalities is recommended as a first line. Pharmacological agents for treatment of primary hyperparathyroidism in pregnancy has not been adequately studied.
Parathyroidectomy in the second trimester is often recommended as definitive treatment.

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P160

PARADIGHM: a natural history registry for patients with chronic hypoparathyroidism

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Chronic hypoparathyroidism affects ~2.5/10 000 individuals in the European Union and is classified as a rare disorder. There is limited knowledge of the natural history and epidemiology of this disease. Publications frequently represent a single center's experience and information across the population of patients with hypoparathyroidism is lacking and needed. To fill the gap, a voluntary global hypoparathyroidism patient registry (PARADIGHM) was initiated by NPS Pharmaceuticals, Inc. The goal is to characterize the epidemiology, natural history, and clinical features of hypoparathyroidism globally and long term.
PARADIGHM is a global, prospective, observational registry based on clinical practices. Patients of any age who have hypoparathyroidism are eligible for inclusion, regardless of etiology or treatment received. Recruitment is planned for 7 years with minimum follow-up of 10 years. Target sample size is 900. Patient enrollment is voluntary through physicians qualifying as investigator sites. Data collected include i) hypoparathyroidism-relevant clinical features and treatment history extracted from medical records, ii) patient-reported outcomes and healthcare use, and iii) mortality.
Registry enrollment began in the USA in July 2013 and is targeted to begin in the European Union in 2014. In addition to baseline demographics, family and medical history, and hypoparathyroidism characteristics and treatment, we expect to report changing features of the disease during follow-up. This includes patients' signs, symptoms, and medical test results; management practices and disease control; risks of clinical events (eg, hypercalcemia or organ impairment); patient quality of life; disease impact on work; hospitalization and emergency room use; and mortality.
PARADIGHM™ will provide previously unavailable long-term, prospective data from a large sample of patients with hypoparathyroidism. Findings will assist providers in clinical decision making through enhanced understanding of the variability and progression of hypoparathyroidism.

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P161

Cinacalcet in the treatment of primary hyperparathyroidism

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Primary hyperparathyroidism is currently recognized with increasing frequency by routine calcium measurement in biochemical examinations. Primary hyperparathyroidism may be due to a parathyroid adenoma, parathyroid hyperplasia and, rarely, parathyroid carcinoma. Cinacalcet is used in the medical management of primary hyperparathyroidism.
The aim was to assess the role of cinacalcet in the treatment of primary hyperparathyroidism.

Patients with primary hyperparathyroidism ($n=20$; aged 56–85 years) were studied. Amongst them four patients had parathyroid hyperplasia and 16 had a parathyroid adenoma. Calcium and PTH levels were increased in all patients. All patients had ultrasonography and a $^{99\,m}$Tc-Sestamibi scan. In 16 patients a parathyroid adenoma was observed either on ultrasound or on scanning or in both. In four of the patients a parathyroid adenoma was not localized by imaging. Cinacalcet was used in all 16 parathyroid adenoma patients to normalize serum calcium levels prior to surgery. In ten of the parathyroid adenoma patients the adenoma was surgically excised, in a female aged 56, hyperparathyroidism recurring a year after surgery. Sequentially, cinacalcet was administered at a dose of 30 mg twice daily and serum calcium levels normalized. Within the group of patients with a parathyroid adenoma six were elderly, aged >75 years, with comorbidity and Cinacalcet was administered at a dose of 30 mg twice daily in 3 and 60 mg twice daily in one to avoid surgery. In the group of patients with parathyroid hyperplasia cinacalcet was used for the treatment of hypercalcemia. Within the whole group, two patients experienced mild gastrointestinal symptoms, but discontinuation of the drug could be avoided.
Cinacalcet may be used for the treatment of primary hyperparathyroidism. It can be used for the normalization of serum calcium prior to surgery, if surgery is not an option, in the event of recurrence after surgery and in parathyroid hyperplasia.

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P162

Hypocalcemia caused by type 1b pseudohypoparathyroidism

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Introduction
The pseudohypoparathyroidism (PHP) encompasses a heterogeneous group of diseases characterized by end-organ resistance to parathyroid hormone (PTH). PHB type 1b (PHP1b) presents with PTH resistance at the renal proximal tubule, sometimes with TSH resistance, usually in the absence of Albright's hereditary osteodystrophy (AHO) clinical features.
Case report
A 64-year-old male was referred to endocrinology department for hypocalcemia. He was the third of eight children of non-consanguineous parents. His psychomotor development was unremarkable. He had a stroke at the age of 50 and suffers from anxiety disorder, hypertension and dyslipidemia. He complains of arthralgia, muscle contractures and paresthesias. A physical examination revealed overweight and short stature (weight 76 kg and height 160 cm), short neck and rounded face, without brachydactyly, subcutaneous calcifications or other signs of AHO. Laboratory tests confirmed hypocalcemia (ionized calcium 0.9 mmol/l) and hyperphosphatemia (5.7 mg/dl) in the presence of elevated PTH (287.3 pg/ml), low calciuria and phosphaturia with normal renal function. Thyroid function tests revealed no abnormalities. Spinal X-ray showed osteophytosis with ossification of the posterior longitudinal ligament. Renal ultrasound revealed nephrolithiasis and brain computed tomography presented calcification of basal ganglia and cerebellum. Five of his brothers (living abroad) have similar analytical results. Routine laboratory tests of the oldest brother, who died in our hospital from brain cancer, also shows hypocalcemia (ionized calcium 0.51 mmol/l) and hyperphosphatemia (6.1 mg/dl). The genetic study of our patient revealed abnormal methylation pattern of exon A/B in *GNAS1* gene associated with heterozygous deletion within STX16 (the gene encoding syntaxin-16), cause of PHP1b, autosomal dominant.
Conclusion
PHP1b is an uncommon disorder that should be considered if there is hypocalcemia, hyperphosphatemia and elevated PTH, particularly in the absence of physical findings consistent with OHA. The autosomal dominant familial form is relatively rare and its recognition may allow early diagnosis and treatment of the disease in other family members.

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P163

Persistant hypercalcemia due to an atypically localised parathyroid adenoma in a patient operated from parathyroid carcinoma: a report of case

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Introduction
Patients with parathyroid carcinoma (PCA) and synchronous disease in other parathyroid glands have been reported in the literature. Here, we report a patient who had persistant hypercalcemia after operated from parathyroid carcinoma and improvement of hypercalcemia after the subsequent operation from atypically localised parathyroid adenoma.
Case report
A 62-year-old man presented with a history of headache, fatigue, and nervousness. Laboratory investigation demonstrated hypercalcemia (11.1 mg/dl) and elevated parathyroid hormone (PTH) level (528 pg/ml). Neck ultrasound revealed multinodular goiter and a $12\times24\times44$ mm parathyroid tumor adjacent to the left thyroid lobe. Because of the cystic components of the parathyroid mass in the ultrasound, parathyroid cancer was suspected. A sestamibi scan was negative. An en bloc resection of the parathyroid mass, and total thyroidectomy was performed. Histopathological examination showed parathyroid carcinoma. Serum calcium and PTH levels were persistently elevated in the postoperative follow-up period. Neck ultrasound was performed and a 8 mm hypoechoic lesion suspicious for in the right parathyroid region was detected. In whole body sestamibi scintigraphy there was an increased uptake in the right parathyroid region. Second operation was not successful for excision of adenoma. On the 10th month of the first operation his calcium was 11.1 mg/dl and PTH 251 pg/ml. Sestamibi/SPECT/CT and neck CT was revealed a lesion in the toracic inlet. The patient underwent third operation and parathyroid adenoma-like lesion was excised distal to the brachio-cephalic artery and bifurcation of common carotid artery and subclavian artery. Histopathological evaluation was parathyroid adenoma. The patient became hypocalcemic on his first postoperative day and treated with i.v. and oral calcium, calcitriol. He was eventually discharged with oral calcium and calcitriol supplementation.
Conclusion
Synchronous parathyroid carcinoma and parathyroid adenoma are extremely rare. The presence of concurrent disease in other parathyroid glands must be kept in mind.

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P164

The child with Di George syndrome born to a mother with primary hypothyroidism diagnosed during pregnancy

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Di George syndrome is, in 93% of cases, the result of spontaneous mutations within the chromosome 22. Environmental factors may affect its occurrence. Phenotypic characteristics of Di George syndrome in children of alcohol-abusing or treated with izotretionin mothers were described. The case of a baby with Di George sndrome born to a woman with symptomatic hyperparathyroidism during her pregnancy is presented.
Case report
A 30-year-old woman at 27 weeks of gestation was admitted to the hospital because of polyhydramnios, weakness, pain and increasing edema of lower limbs. Calcium, 14.7 mg/dl; PTH-1244 pg/ml, 25OH; vitamin D, 6.5 ng/ml, normal renal function were found in laboratory studies. An USG of neck revealed a hypoechogenic structure 20×15 mm below the lower pole of the right thyroid lobe. The diagnosis of primary hyperparathyroidism was established. Numerous bone lesions with the nature of brown tumors were found in the studies performed

after birth. Scintigraphic examination confirmed the presence of enlarged parathyroid glands. Having given birth, she underwent a surgery leading to the normalization of calcium metabolism. At 31 weeks of gestation, due to the premature rupture of membranes, cesarean section was performed. The patient gave birth to her first child, female (5/5/7 point. Apgar). On the 11th day of life, diarrhea developed and electrolyte disturbances (hipocalcemia 4.4 mg/dl and hypomagnesemia 1.0 mg/dl) were observed. Genetic testing for Di George syndrome was performed because of the identified clinical features: a small typical dysmorphia, regurgitation through the nose, lack of thymus in USG, low PTH level. The diagnosis was confirmed. Genetic testing of the child's parents did not show the presence of any mutations.

Conclusions

i) It is interesting whether chronic hypercalcemia in the mother could have an impact on the presence of mutations in the child. ii) To our knowledge, this is the first report of the coexistence of maternal Di George syndrome and primary hyperparathyroidism in a child.

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P165

Evaluation of vitamin D concentration in a population of young, healthy women: effects of vitamin D supplementation

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Vitamin D and calcium are necessary for proper modelling and remodelling of osseous tissue and optimal bone mass depends on their appropriate supplementation.

Aim of study, materials and methods

The goal of the study was an evaluation of serum vitamin D concentrations (vit. D) in 106 healthy women, aged 20–30 years plus a monthly evaluation – for 3 months – of the effects of calcium (500 mg) and vit. D (1500 IU) administration in women with baseline values of vit. D <20 ng/ml (Group 1) plus the effects of 800 IU/day dose in women with the baseline value of D >20 ng/ml (Group 2). Additionally, calcium and PTH concentrations were assessed at the study onset and after the 3-month supplementation.

Results

The mean vit. D concentration in entire study group was 16.55 ng/ml, being 12.6 ng/ml in the Group 1 and 25.23 ng/ml in the Group 2. In the course of vit. D administration, its concentration increased statistically significantly, both in the entire group and in the subgroups, at all time points vs the study onset ($P<0.001$). Moreover, the concentration increase was statistically significant after 2 and 3 months, both in the entire group and in the Group 1. Similarly, in the Group 2, the vit. D concentration was systematically rising in the course of the observation but the statistically significant increase was noted vs. the baseline point. Although there were no differences in calcium concentration after the 3 months, a statistically significant drop of PTH ($P<0.05$) was recorded in the entire population and in the Group 1.

Conclusions

A moderate deficit of vit. D was observed in the studied population of young women. A supplementation with calcium plus vitamin D brought about an increase of vitamin D concentration already in the 1st month of administration. The optimal concentration of >30 ng/ml was achieved in the Group 1 after 3 months of vitamin D administration in the 1500 IU/day dose.

The study was supported by Axellus LLC (Poland).

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P166

Do Lithuanian military conscripts suffer from hypovitaminosis D?

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The aim of the study was to evaluate vitamin D levels in Lithuanian male military conscripts and its association with PTH, osteocalcin and testosterone, body muscles and LBM percentage, as well as depression–sadness, tension–anxiety and psychological and physical quality of life.

Methods

A total of 262 healthy Lithuanian male military conscripts were tested for vitamin D, PTH, osteocalcin and testosterone concentration and 155 (59.2%) of them we rechecked 1 year later. Paralleled body composition was performed by the principle of bioelectrical impedance and evaluation of emotional state (POMS) as well as quality of life. Results. Primary vitamin D deficiency (<20 ng/ml) was detected in 95.0 and 96.7% when rechecked. The mean concentration of vitamin D was 12.5 ± 4.5 and 10.4 ± 4.9 ng/ml 1 year later. Nevertheless, PTH (2.54 ± 1.23 pmol/l) and osteocalcin (38.9 ± 11.9 ng/ml) concentration when checked and rechecked (2.70 ± 1.10 pmol/l and 40.4 ± 12.8 ng/ml, respectively) were in normal ranges. Spearman's rank order correlation ($r=-0.2$; $P=0.02$) between vitamin D and PTH was detected when rechecked at the end of military service. At the end of the study, vitamin D concentration correlated with muscles ($r=0.2$; $P=0.03$) and LBM percentage ($r=0.2$; $P=0.04$), and the mean testosterone concentration was significantly ($P=0.025$) lower in severe vitamin D deficiency (<10 ng/ml) if compared with moderate (10–20 ng/ml) – 16.7 ± 4.13 and 18.6 ± 5.08 nmol/l, respectively. Vitamin D concentration correlated negatively with tension–anxiety ($r=-0.14$; $P=0.03$) and depression–sadness ($r=-0.19$; $P=0.03$) and positively with quality of life: Physical health ($r=0.27$; $P=0.0009$) and psychological health ($r=0.29$; $P=0.0005$).

Conclusion

The majority of the Lithuanian male military conscripts were detected to have vitamin D concentrations, corresponding severe deficiency. The greater vitamin D deficiency at the end of the study resulted in significant increase in PTH concentration; however, there were no significant changes in the osteocalcin concentration. More severe vitamin D deficiency at the end of the study significantly correlated with a smaller amount of body muscles and LBM percentage and decreased testosterone concentration. A lower vitamin D concentration conditioned depression–sadness and tension–anxiety as well as decreased psychological and physical quality of life.

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P167

Unusual case of intrathyroid parathyroid hyperplasia revealed by parathyroid hormone determination in fine-needle aspirate, co-existing with multifocal papillary thyroid carcinoma

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Introduction

Ectopic parathyroid tissue is a rare cause of primary hyperparathyroidism (PHPT). Intrathyroid location has been reported in 18–33% of cases.

Case report

A 67-year-old Caucasian female was admitted for evaluation of multi-nodular goiter and normocalcaemic PHPT. The patient was asymptomatic; her medical history was remarkable for hypertension, dyslipidaemia, and albuminuria. Her family history has positive for albuminuria.

Physical examination showed diffuse goiter and a palpable nodule at the left thyroid lobe. Initial laboratory assessment showed: corrected total serum calcium: 9.4 mg/dl (normal: 8.8–10.6), serum phosphorus: 3.1 mg/dl (normal: 2.5–4.5), PTH: 86 pg/ml (normal: 10–53), 25-hydroxyvitamin-D: 38 ng/ml (normal: >30), TSH: 0.59 mIU/l (normal: 0.4–4), calcitonin: 1 pg/ml (normal: <10), estimated glomerular filtration rate: 65 ml/min per 1.73 m^2, 24 h-urinary calcium: 164 mg/24 h (normal: 0–250).

Neck ultrasound revealed a 10×8.6 mm bean-shaped hypoechoic lesion, two hypoechoic nodules <7 mm and one with microcalcifications (7×5.2 mm) in the right lobe. A 21×18 mm isoechoic nodule ('hot' on thyroid scan), two hypoechoic nodules (10 and 7 mm) and one with microcalcifications (8×5 mm) were found in the left lobe. No abnormal lymph nodes were observed. Renal ultrasound was normal.

Ultrasound-guided fine-needle-aspiration-biopsy (FNA-b) was performed in the nodules with microcalcifications and the bean-shaped one. PTH was measured in the aspirate of the latter. Cytopathology showed 'atypia of undetermined significance' (BETHESDA III), while PTH-washout concentrations were 1900 pg/ml.

The patient underwent total thyroidectomy, showing bilateral multifocal papillary thyroid carcinoma (PTC) with microscopic invasion of perithyroidal tissue, two right parathyroid glands with hyperplasia (one intrathyroid) and one normal left gland.
Postoperatively, PTH levels did not normalize, calcium remained normal and the patient was referred to adjacent radioiodine ablation.
Conclusions
This is the second case of intrathyroid parathyroid gland co-existing with PTC. Parathyroid FNA-b with PTH washout may be a useful diagnostic tool in such cases.

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P168

Vitamin D deficiency and tuberculin skin test reaction in old age home residents in Romania

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Introduction
We studied the relationship between vitamin D deficiency and tuberculin skin test (TST) to assess the delayed cellular immunity in older age home residents.
Design
This was a case–control study.
Methods
We evaluated TST in 50 nursing home residents (35 women and 15 men, aged 58–89 years) with 25-hydroxyvitamin D (25(OH)D) concentrations <50 nmol. A one-stage TST was performed using 0.1 ml of PPD RT23. An induration $\geqq 10$ mm was considered as positive.
Results
Most patients (68%) had vitamin D deficiency (25(OH)D <30 nmol/l). After one-step testing, 40% of residents had positive TST reactions. The total number of leukocytes was significantly higher in TST-positive patients than in those with negative response. Linear regression shows a significant association between induration diameter and patient age (the diameter decreases with age). Linear regression shows a significant association between the induration diameter and the total number of leukocytes (the diameter increases with total leukocytes) and between the diameter and the percentage of neutrophils (the diameter decreases with the percentage of neutrophils). There was no significant correlation between serum concentrations of 25(OH)D and tuberculin reaction.
Conclusion
The present study showed no correlation between serum concentrations of 25(OH)D and TST reactions, but this could be explained in the context of vitamin D deficiency present in all patients included in the study.

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Cardiovascular Endocrinology & Lipid Metabolism

P169

Cardiothyreosis: pathogenic conjectures, clinical aspects and surgical approach

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Background
The presence of striking cardiovascular manifestations was noted in the first descriptions of hyperthyroidism owing to Parry (1825) and Basedow (1840) in the famous Merseburger triad. Hyperthyroidism may either cause cardiac complication in individuals with a normal myocardium (genuine form of disorder) or complicate pre-existing cardiac troubles.
Patients and methods
An homogenous series of 49 cardiothyreosis, 11 males and 38 females, aged 12–78 (mean 45) years selected between 136 thyrotoxic cases operated on in a period of two decades is herein presented. There were registered 15 Basedow diseases, 16 toxic adenoma and 18 multinodular toxic goitres. Among these were found isolated or dominating when combined together ten cases with cardiac failure, 21 cases with rhythm troubles (four with extrasis tolic arrhythmia and one with fibriloflutter) and nine cases with coronary insufficiency. To these seven hypertensive patients and two cases with mitral valvulopathy were added. In hyperthyroidism clinical diagnostic was confirmed on imaging exams and hormonal determinations while cardio-vascular disturbances was ascertained by interogatory, physic signs, EKG and echocardiography. All our cases were operated on performing 33 near total thyroidectomies and 16 lobectomies without mortality recording yet three postoperative tachyarrhythmias but finally most of them with good clinical results (89.8% cured or significantly ameliorated).
Discussions and conclusions
Pathogenic diagnosis of such so-called 'cor thyreotoxicum' is not always easy on account of cardiovascular syndrome which frequently overshowed the thyroid subclinical picture or emergence of new entities as amiodarone induced thyrotoxicosis. In the treatment of cardiothyreosis pharmacologic management realized only transient and in-stable results and radical thyroeliminating procedures should have preference. The single administration of a whole calculated dose of I^{131} with subsequent treatment with thyrostatics and β-blockers till remission of thyrotoxic is achieved can be chosen opposing to thyroidectomy after short medicamentous preparation which is effective in large thyromegalies and toxic adenoma.

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P170

Polyphenol-rich dark chocolate lowers LDL oxidation without affecting high-sensitivity CRP levels in adults

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Chronic inflammation and oxidative stress have been described as crucial factors in the pathogenesis of atherosclerosis and the occurrence of cardiovascular diseases (CVD). Polyphenols are phytochemicals with established antioxidant properties, and dark chocolate (DC), a highly consumed food, is one of main food sources of polyphenols. Many human studies have suggested a lowering effect of DC on oxidized LDL levels, while its impact on high sensitivity CRP (hs-CRP) -one of the most powerful predictors of coronary artery diseases- are still conflicting. The aim of this study is to determine the preventive properties of (polyphenol-rich DC) PRDC on CVD by testing its effects on hs-CRP and oxidized LDL levels. 54 participants (18–58 years) with no history of diabetes, hypertension or CVD took part in a 4-week randomized parallel clinical trial. Participants were assigned daily either 20 g of a placebo DC (with negligible amount of polyphenols; 27 participants) or a PRDC (500 mg of polyphenols; 27 participants). Blood samples were collected at baseline and after 4 weeks. In the PRDC group, results showed a significant decrease in oxidized LDL levels (6.65 ± 16.13, $P=0.042$), while no significant changes in hs-CRP levels were observed ($P=0.23$) following the intervention. The decrease in oxidized LDL was not associated with a decrease in LDL levels ($P=0.92$), and no significant changes in the placebo DC group were noted. These outcomes correspond to the findings of the literature which mostly showed a positive effect of PRDC on LDL oxidation, possibly due to the effects of some polyphenols on scavenging oxygen species. The neutral effects on hs-CRP levels fairly match with many intervention trials on cocoa/DC and inflammation. This suggests that further studies controlling for potential confounding factors and drawbacks affecting the reliability of this marker are needed before refuting a positive effect of PRDC on inflammation.

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P171

Osteopontin, hs-CRP levels in gestational diabetes mellitus

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Introduction
Gestational diabetes mellitus (GDM) is a sort of temporary carbonhydrate intolerance in pregnancy. GDM leads to a variety of risks for the fetus and the mother during pregnancy. Mothers who had GDM during their pregnancy have

high risk of caesarean section and pre-eclampsia. Also there are risks of macrosomia, neonatal hypoglycemia and hyperbilirubinemia for the fetuses of these mothers. Cardiovascular disorders, hypertension, dyslipidemia and metabolic syndrome are the other diseases that can develop in years after GDM. In the literature, OPN is known to have an important role in the development of atherosclerosis, vascular calcification and remodeling. The aim of this study was to evaluate osteopontin (OPN) and high sensitive CRP (hs-CRP) levels in GDM patients.
Methods
33 patients with GDM and 26 control patients pregnant were included in this study. Blood tests for lipid profile, fasting glucose, oral glucose tolerance test, OPN, HOMA-IR, hs-CRP were done at nearly 24th gestational week. Serum levels of OPN were measured by ELISAs, and serum hs-CRP levels were measured by particule association turbidometric assay.
Results
The gestational week, age, BMI of two groups were similar ($P > 0.05$). The GDM group had significantly higher fasting glucose, prandial (first and second h) glucose, HbA1c levels than the control group. Fasting insulin, HOMA-IR levels were higher in the GDM group than the control group but the difference was not significant. The lipid profiles of two groups were not significantly different. The OPN levels were 3.4 (2) ng/ml in the GDM group and 3.05 (1.6) ng/ml in the control group ($P < 0.05$). The hs-CRP levels were also significantly higher in the GDM group compared with the control group (0.85 (0.7) vs 0.4 (0.3), $P < 0.05$).
Conclusion
OPN and hs-CRP levels were significantly increased in GDM patients.

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P172

Isotretinoin effect on osteopontin, hs-CRP, insulin sensitivity and CIMT in acne patients

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Introduction
Isotretinoin (Iso) treatment in acne disease may cause dyslipidemia and increased liver enzymes. Its effects on lipid and glucose metabolism may cause atherogenic complications. The aim of this study was to evaluate carotis intima–media thickness (CIMT), HOMA-IR, and osteopontin (OPN) levels in acne patients on Iso treatment.
Methods
Iso treatment given 21 patients are included in this study. They followed for 4 months. 21 patients with acne were given Iso (0.5–0.8 mg/kg) for 4 months. Blood tests for lipid profile, fasting glucose, liver enzymes, OPN, HOMA-IR, hs-CRP, and CIMT measurements were done before and after Iso treatment. Serum levels of osteopontin, hs-CRP were measured by ELISA and by particule association turbidimetric assay respectively.
Results
Iso treatment significantly caused dyslipidemia, increased CIMT (0.60–0.74 mm; $P < 0.05$), while it non-significantly increased HOMA-IR (0.91–1.87; $P > 0.05$), OPN (4.32–5.44 ng/ml; $P > 0.05$), and hs-CRP (0.08–0.09 mg/dl; $P > 0.05$) levels.
Conclusions
Iso treatment in acne patients increased the risk of atherosclerosis probably by causing dyslipidemia but it also, albeit non-significantly increased OPN, hs-CRP, and HOMA-IR levels.

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P173

New vitamin D less-calcemic analog affects human bone cell line and cultured vascular smooth muscle cells similar to other analogs

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Aim
The aim of our study is to assess the efficacy of a lifestyle modification including altered diet composition and physical activity in preventing diabetes mellitus type 2 (DM2) in individuals with impaired glucose tolerance and impaired fasting glucose (IGT/IFG) and influence it on changes serum leptin levels.
Materials and methods
The study included 327 patients with IGT/IFG (68 m, 258 f) 25-65 years. Patients were divided into two groups matched by sex, age, weight, and BMI. Research group included 183 patients (32 m, 150 f) who received and carried out individual recommendations of a balanced diet and physical activity. Control group included 144 patients (36 m, 108 f) who did not lifestyle modification. Related to fasting leptin (FL) concentrations by sensitive ELISA.
Results
Patients of the research group demonstrated reduction of body weight ($P < 0.01$). They had positive dynamics of FPG and 2-h PG concentrations also ($P < 0.001$). Persons of the control group had significant increase in weight and BMI and FPG and 2-h PG concentrations elevated ($P < 0.05$). 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. Among patients of the research group was a reduction of new care 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, postprandial glucose concentrations but and fasting leptin concentrations in individuals with IGT/IFG.

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P174

Oxytocin prevents cardiomyocyte hypertrophy

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Aims/hypothesis
Oxytocin (OT) and OT receptor (OTR) are expressed in the heart. During OT synthesis, its precursor, termed OT-Gly-Lys-Arg (OT-GKR), is abundantly accumulated in the developing rat heart. Because the OTR is primarily associated with Gq/11protein subunit that activates protein synthesis, we hypothesised that OT can cause cardiomyocyte hypertrophy. On the other hand, OTR signalling is associated with anti-hypertrophic atrial natriuretic peptide (ANP) release and nitric oxide (NO) activation in the heart. Consequently, we investigated whether OT treatment promotes or inhibits hypertrophy in cardiomyocytes.
Methods
The experiments were carried out in newborn and adult rat cardiomyocyte cultures. The enhanced protein synthesis and increased cardiomyocyte volume were stimulated by a 24 h treatment with endothelin-1 (ET-1) or angiotensin II (Ang II).
Results
Treatment with OT or OT-GKR did not increased [^{35}S]-methionine incorporation by cardiomyocytes and not changed cell volume during 24–72 h. The treatment of newborn rat cardiomyocytes with OT or its abundant cardiac precursor, OT-GKR, revealed ANP protein and increased intracellular cGMP accumulation. Consequently, the cardiomyocyte hypertrophy related to ET-1 and Ang II was abolished by the treatment of 10 nM OT or 10 nM OT-GKR. The ANP receptor blockade by anantin and NO synthases by L-NAME, inhibited cGMP enhancement in cardiomyocytes exposed to OT. In the presence of inhibitors STO-609 and compound C the anti-hypertrophic OT effects in cardiomyocytes was reduced which suggest that OT signalling includes activation of calcium–calmodulin kinase kinase and AMP-activated protein kinase pathways. Moreover, in ET-1 stimulated cells, OT treatment normalized reduced Akt phosphorylation, prevented abundant accumulation of ANP and blocked ET-1-mediated translocation of nuclear factor of activated T-cells (NFAT).
Conclusion
cGMP/protein kinase G mediates OT-induced anti-hypertrophic response with the contribution of ANP and NO. OT treatment represents a novel approach in attenuation of hypertrophy during development and cardiac pathology.

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P175

Parameters of metabolic syndrome in prehypertensive subjects: should we be looking for them?

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Introduction
Insulin resistance has been found to be higher in hypertensive subjects. Whether this is also true in prehypertension is controversial. We examined both insulin resistance and lipidemic profile in subjects with prehypertension.
Methods
214 outpatients (119 men and 97 women) of Greek origin were divided into two groups: i) prehypertensive and ii) control group. These groups were tested for insulin resistance using the HOMA-index, as well as lipids values. All participants were matched for age and BMI. Prehypertension is defined as BP = 120–139/80–89 mmHg and normal BP < 120/80 mmHg. Ambulatory blood pressure was measured in both groups. Categorical and numeric values were analyzed with χ^2 and *t*-test or Mann–Whitney *U*-test were appropriate.
Results
HOMA-index was higher in the prehypertensive versus the control group ($P = 0.013$), and similar results were shown for the measurement of insulin ($P = 0.001$). Additionally, a statistically significant difference was found between the control versus the prehypertensive group for cholesterol ($P = 0.017$) and triglycerides ($P = 0.003$). No significant differences were found for all the other parameters.
Conclusions
Our study revealed a significantly higher Insulin resistance, total cholesterol and triglyceride the prehypertensives. These are parameters of the metabolic syndrome, which is associated with the high cardiovascular risk. Thus, measuring these factors might be useful people with non-optimal values of BP.

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P176

Serum and plasma aldosterone levels and the respective aldosterone/plasma renin indices in healthy blood donors

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Introduction
Primary aldosteronism (PA) is one of the causes of hypertension. Blood aldosterone and the aldosterone/direct renin concentration (DRC) are routinely used as a screening test for PA.
Aim of study
Whether it matters if aldosterone concentration is determined in serum or plasma samples?
Material and methods
145 healthy males, five females (blood donors) were investigated. In all subjects blood was collected into two tubes: one in EDTA2K (plasma) and one with clot activator (serum). Aldosterone was measured by RIA kit (ZenTch, Belgium), and renin by immunoradiometric kit (CIS bio, France).
Results
In blood donors, the median (and the range) of aldosterone concentration determined in serum was 145 pg/ml (56–369 pg/ml) and in plasma – 289 pg/ml (172–664 pg/ml). These differences ranged 41–75% (median 50%). Correlation between aldosterone in serum and plasma was $r = 0.9089$; $r^2 = 0.9385$; $P < 0.01$, but plasma aldosterone levels appeared significantly higher in relation to serum aldosterone levels ($P < 0.0001$).
The median and the range of serum aldosterone to plasma DRC indices was 13 (2–45) and of plasma aldosterone to plasma DRC – 26 (5–99). These differences ranged 31–68% (median 50%). Correlation between both indices was $r = 0.9523$; $r^2 = 0.9429$; $P < 0.0001$, but plasma aldosterone/DRC indices appeared to be significantly higher than serum aldosterone/DRC indices ($P < 0.0001$).
Conclusions
i) Marked differences between the serum and plasma aldosterone levels demand application of separate reference ranges.
ii) Aldosterone/DRC indices may differ significantly depending on whether aldosterone levels are measured in serum or plasma.

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P177

Red wine increases SHBG production by HepG2 cells

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Low circulating sex hormone-binding globulin (SHBG) is an independent risk factor for cardiovascular disease. Mediterranean diet has been associated with a decreased risk of cardiovascular disease. We have recently shown that olive oil consumption is associated with elevated SHBG serum levels and that PPARγ downregulation induced by oleoyl-CoA is an important underlying mechanism of such regulation. Red wine is also an important component of the Mediterranean diet and its moderate consumption has health benefits on cardiovascular and metabolic disease. The aim of the present study was to investigate whether treatment with red wine could increase SHBG levels in HepG2 cells and the molecular mechanisms involved. We performed treatments in HepG2 cells with red wine, white wine or ethanol (as a control) during 3 days. Our results showed that red wine treatment increased SHBG (mRNA and protein) when compared with white wine and ethanol treatments in HepG2 cells. Since the concentration of the polyphenolic compound resveratrol in red wine is higher than in white wine, we next wanted to study if resveratrol could increase SHBG production over the course of 3 days in HepG2 cells. The results showed that resveratrol (10 or 25 μM) treatment was able to increase SHBG levels (mRNA and protein) in a dose-dependent manner when compared with vehicle-treated HepG2 cells. This effect was not mediated by HNF4α and PPARγ, two important transcription factors involved in SHBG regulation. In conclusion, resveratrol, a component of red wine, increases SHBG production in HepG2 cells. Our results suggest that the cardioprotective effect of red wine could be mediated in part by increasing SHBG levels. However, further studies are needed to elucidate the exact molecular mechanisms underlying SHBG upregulation by resveratrol.

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P178

New possible predictors of left ventricular hypertrophy

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Introduction
Left ventricular hypertrophy (LVH) in obesity cannot be explained only by increased body mass (BM), BMI, or arterial hypertension (AH). Aim was to investigate possible clinical or hormonal predictors of LVH.
Materials and methods
We examined women before The Programme of Weight Loss. The echocardiography was performed; mass of myocardium of LV (MMLV), relative wall thickness (RWT) and indexed MMLV (IMMLV) by body surface area were calculated. LVH was diagnosed when IMMLV ≥ 95 g/m^2, increased RWT - RWT ≥ 0.42. Fasting insulin, leptin and adiponectin were measured.
Results
Data of 113 women (age = 44.34 ± 11.18 years, BMI = 35.00 ± 5.22 kg/m^2) were evaluated. 67 women had LVH (59.3%), 56.5% of them had AH ($P = 0.010$). Insulin, leptin and adiponectin did not differ in women with or without LVH. Patients with enlarged RWT had increased levels of leptin (55.14 ± 30.24 vs 42.60 ± 24.17 ng/ml, $P = 0.041$) and decreased levels of adiponectin (10.12 ± 0.56 vs 12.94 ± 0.72 mkg/ml, $P = 0.050$). In multinominal regression age ($\beta = 1.67$, $P = 0.005$), BM ($\beta = 2.63$, $P = 0.004$) and mean blood pressure (BP) ($\beta = 1.07$, $P = 0.009$) were predictors of increased MMLV; age ($\beta = 0.83$, $P = 0.006$) and mean BP ($\beta = 0.56$, $P = 0.007$) were also positive predictors of increased IMMLV. In logistic regression age (OR = 1.07, $P = 0.024$), BM (OR = 1.08, $P = 0.023$), AH (OR = 34.7, $P = 0.038$), waist circumference (OR = 0.92, $P = 0.038$) and adjusted by AH BMI (OR = 0.12, $P = 0.042$) were predictors of LVH, whereas only adiponectin level was a positive predictor of increased RWT (OR = 2.80, $P = 0.039$).
Conclusion
Adiponectin and leptin may be also positive predictors of increase of LV mass as age, BM and AH.
Keywords
Left ventricular hypertrophy, adiponectin, leptin.

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P179

Characteristics of compensated hypogonadism in patients with sexual dysfunction

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Introduction
In the last few years the view that subclinical endocrine disorders represent milder forms of the clinically overt disease has emerged. Accordingly, it has been proposed that compensated hypogonadism represents a genuine clinical subgroup of individuals with late onset hypogonadism (LOH). The aim of the present study is to investigate the association of compensated hypogonadism with clinical and psychological characteristics of male subjects complaining for sexual dysfunction.
Methods
After excluding documented genetic causes of hypogonadism, an unselected consecutive series of 4173 patients consulting our Unit for SD was studied. Compensated hypogonadism was identified according to the European Male Aging Study criteria: total testosterone = 10.5 nmol/liter and LH >9.4 U/L. Several hormonal, biochemical, and instrumental (penile Doppler ultrasound) parameters were studied, along with a structured interview on erectile dysfunction (SIEDY), and ANDROTEST.
Results
170 (4.1%) subjects had compensated hypogonadism, whereas 827 (19.8%) had an overt hypogonadism. After the adjustment for confounding factors, non-specific sexual symptom was related to compensated hypogonadism. However, compensated hypogonadism individuals more often reported psychiatric symptoms, as detected by ΣMHQ score, when compared to both eugonadal and overt hypogonadal subjects (adjusted OR = 1.018[1.005;1.031]; 1.014[1.001;1.028]; both $p < 0.005$). In addition, subjects with compensated or overt hypogonadism had an increased predicted CV risk (as assessed by Progetto Cuore risk engine) when compared to eugonadal individuals. Accordingly, major adverse cardiovascular events (MACE)-related mortality, but not MACE incidence, was significantly higher in subjects with both compensated and overt hypogonadism, when compared to eugonadal subjects.
Conclusions
Present data do not support the concept that compensated (subclinical) hypogonadism represents a new clinical entity. In fact, subclinical low T may be considered as a resilient response to adverse conditions, such as CV diseases, that naturally restrain reproductive and sexual activity. Further studies are urgently needed to clarify this latter point.

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P180

Blood levels of apelin in patients with essential hypertension and type 2 diabetes mellitus and its relationship with the duration of hypertension and anthropometric indices

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Introduction
Endogenous peptide apelin has profound hypotensive and inotropic effects, improves glucose utilization, which emphasizes its importance in the pathogenesis as essential hypertension (EH) and type 2 diabetes mellitus (T2DM). The aim of this study was to investigate the blood levels of apelin in patients with EH in combination with T2DM.
Description of methods/design
The examination involved 19 patients with EH grades 2–3 with T2DM (eight men and 11 women), aged 43–70 years. The investigation complex included measuring anthropometric indices, levels of fasting blood glucose, lipid profile, fasting blood insulin with insulin resistance index calculation (HOMA index). The blood level of apelin-12 was tested using an ELISA. The control group consisted of 12 practically healthy people.
Results
Blood levels of apelin-12 in the patients with EH and T2DM were significantly lower compared to healthy volunteers – 0.866 (0.788; 0.992) ng/ml vs 1.087 (0.861; 1.318) ng/ml, $P < 0.05$. Correlation analysis in the whole group of patients showed a significant correlation between blood levels of apelin-12 with a duration of EH ($r = -0.56$, $P < 0.05$). Gender differences in blood levels of apelin-12 in the patients or in the healthy people were not found. In males with EH and T2DM blood level of apelin-12 was significantly correlated with body weight ($R = +0.92$, $P < 0.01$), BMI ($R = +0.79$, $P < 0.05$), waist circumference ($R = +0.9$, $P < 0.01$) and hips circumference ($R = +0.79$, $P < 0.05$).
Conclusion
The patients with EH and T2DM compared to the healthy subjects have decreasing of blood levels of apelin-12, the degree of which correlates with the duration of hypertension. At the same time, these data suggest that in the male patients with EH and T2DM increased body weight indicators can contribute to the preservation of secretion of the peptide, which is synthesized mainly in the adipose tissue cells.

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P181

Adherence to treatment in hypertension and diabetes

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Objective
To study the effectiveness of therapy and the role of adherence to treatment in patients with DM and AH.
Methods
A 75 patients studied with Moriski-Green test. Psycho-correctional work has been carried out with 37 people (Group 1) in order to increase motivation for treatment, and the work has not been carried out with 38 people (Group 2). The treatment effect has been evaluated after 3 months according the results of sBP and dBP dynamics and 24 h blood pressure monitoring.
Results
Out of 75 patients, 65% appear to be nonadherent to treatment. According to the results of initial examination the data of patients from the groups have no difference. The reduction of sBP, dBP has been reported in both groups after 3 months. According to the results of 24 h BPM, the normalization of average daily and night numbers has been set, as well as sBP and dBP in both groups; and only in the one group there has been noticed the reduction of sBP variability at night, daily index of sBP and dBP, rate of morning sBP and dBP increase, which are high risk indicators of cardiovascular events.

	Before treatment		After treatment			
Indicator (mmHg)	Group 1	Group 2	Group 1	Group 2	*P1*	*P2*
sBP	165.6±17.9	168.6±20.5	130.0±9.8	127.5±10.5	<0.001	<0.001
dBP	102.8±11.1	113.7±9.6	80.0±9.1	69.7±17.5	<0.001	<0.001
Average sBPd	154.3±9.3	156.7±12.2	120.3±7.5	126.7±10.0	0.002	0.001
Average sBPn	138.8±8.7	140.1±8.9	111.4±7.3	112.6±7.1	0.001	<0.001
Average sBPd	94.8±7.7	92.2±10.1	74.4±5.6	71.4±9.3	0.003	0.002
Average sBPn	88.2±6.2	86.9±11.0	66.7±4.6	71.4±9.3	0.005	0.016
Var. sBPd	13.8±3.9	13.3±3.2	13.4±3.2	13.5±3.3	0.462	0.483
Var. sBPn	13.0±2.1	12.6±3.0	11.6±1.8	12.0±2.9	0.024	0.083

Conclusion
Psycho-correctional training improves adherence of patients to treatment, which is accompanied by positive dynamics of 24 h BPM indicators.

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P182

Evaluation of lipid levels in familial hypercholesterolemia in a lipid unit

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Objective
To determine the degree of control of hypercholesterolemia in a specific lipid unit.

Material and Methods
Retrospective study of patients followed in our unit over the past 16 years diagnosed with heterozygous familial hypercholesterolemia (HFH) or familial combined hyperlipidemia (FCH). Control criteria according to the following recommendations were compared: International Panel (2003), Nice (2008), NLA (2011), ESC / ESA 2011, Consensus ADA / American College of Cardiology Foundation.
Results
Data from 111 patients were analyzed: 66 with HFH and 45 with FCH.
Patients with HFH currently 91.4% are taking statins (rosuvastatin 36.2%, atorvastatin 31%) and 57.9% ezetimibe. The total initial and final cholesterol was: 280.9±67.1 vs 196.3±36.6 mg/dl, LDL-C: 194.1±71.2 vs 119.1±35.9 mg/dl, HDL-C: 55.4±12.9 vs. 59.4±16.5, non-HDL-C: 223±72.5 vs 134.7±34.9 mg/dl. The therapeutic goals for LDL were obtained in the following percentages: International Panel: 79.6%; Nice: 55.6%, NLA: 69.3% and ESC/ESA: 37.7%.
85.4% of FCH patients currently are taking statins (46.3% rosuvastatin, 22% fluvastatin), 65.9% fenofibrate, 29.3% omega 3 and 31.7% ezetimibe. The total initial and final cholesterol was: 282.5±63.8 vs 202.1±47.4 mg/dl, LDL-C: 155±41.5 vs 121.4±50.1 mg/dl, HDL-C: 35.5±12.1 vs 47.7±14.9, non-HDL C: 237.7±64.9 vs 151.9±46.9 mg/dl. According to the Consensus criteria ADA / American College of Cardiology Foundation therapeutic goals for LDL-C were achieved in 33.3% and for non-HDL C in 23.5%.
Conclusion
In patients with familial hypercholesterolemia, despite intensive treatment, therapeutic targets set by international guidelines are infrequently achieved.

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P183

Association between serum thyrotropin levels and insulin resistance in euthyroid patients

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Aim
Thyroid hormones act both insulin agonistic and antagonistic in different organs. Studies that evaluate the relationship between insulin resistance and hypo-hyperthyroidism have conflicting results, even euthyroid status was shown to change insulin sensitivity. In this study, our aim is to investigate the association between TSH, free T_4, free T_3 levels and insulin resistance in euthyroid patients.
Method
Euthyroid 57 males, 47 females total 104 patients were involved to study, patients that use any drug that affects thyroid, insulin and glucose levels and have any chronic disease, thyroid disease and obesity were excluded. BMI, fasting glucose levels, insulin levels, lipid profiles of patients were evaluated. Insulin resistance was measured with homeostasis model assessment (HOMA-IR), carotis intima media thickness (CIMT) were measured. Patients were classified as two groups due to TSH levels, the patients with TSH levels below 2 mIU/l were defined as group 1 and patients with TSH levels above 2 mIU/l were defined as group 2. Two groups were compared and correlation analysis were made.
Findings
There was not any significant difference between groups in terms of age, BMI ($P>0.05$). Fasting blood glucose, triglyceride and LDL levels were higher in group 2 but difference was statistically insignificant. Fasting insulin levels and insulin resistance that measured with HOMA-IR method were higher in group 2 when compared with group 1 and these findings were statistically significant (HOMA-IR in group 1; 0.80±0.51, in group 2; 1.63±1.70, fasting insulin levels in group 1; 3.83±2.23, in group 2; 7.56±7.54) ($P=0.003$). There was an positive correlation between TSH levels and HOMA-IR, CIMT (r: 0.46, $P<0.001$ and r: 0.37, $P<0.001$).
Discussion
Our study revealed that even in euthyroid patients normal TSH levels may be related to insulin resistance and an arteriosclerosis indicator CIMT. As TSH values exceeding 2 mIU/l, insulin resistance develops and due to relationship between insulin resistance and ateroscleroses carotis intima media thickness increases as well.These results raise questions whether current normal TSH levels are actually normal? And should it be narrower? To answer these questions more detailed studies with euthyroid population are required.

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P184

Features of patients with familial hypercholesterolemia treated in a specific lipid unit

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Objective
To determine the characteristics of patients with familiar hypercholesterolemia studied in a specific unit of lipids.
Material and methods
A descriptive study of patients followed in our unit over the last 16 years diagnosed with heterozygous familial hypercholesterolemia (HFH) or familial combined hyperlipidemia (FCH).
Results
Data from 111 patients were analyzed: 66 with HFH and 45 with FCH.
Features of patients with HFH were: mean age 49.4±15.8 years, 62.1% females, with a mean follow-up of 7.9±8.7 years. The more frequent reason to start study was the screening from family hypercholesterolemia (44.7%). 25.4% had hypertension, 16.7% diabetes, 18.4% were obese, 22.8% were smokers and 9.1% had prior CVD at first visit. 65.9% had already started treatment prior to our first visit (26.5% atorvastatin and 23.5% simvastatin). Currently 91.4% are taking statins (rosuvastatin 36.2% and atorvastatin 31%) and 57.9% ezetimiba. 69.1% perform daily physical exercise and 67.4% perform diet adequately.
Features of patients with HFC were: mean age 57.7±11.2 years, 60% males, with a mean follow-up of 9.1±7.4 years. The more frequent reason to start study was because incidental finding in analytical (63.9%). 48.9% had hypertension, 42.3% diabetes, 36.4% were obese, 22.5% were smokers and 17.5% had CV events prior to first visit. 48.4% had already started treatment prior to our first visit (21.1% atorvastatin). Currently 85.4% are taking statins (46.3% rosuvastatin and fluvastatin 22%), fenofibrate 65.9%, omega 3 29.3% and ezetimibe 31.7%. 58.3% perform daily physical exercise and 37.5% perform diet adequately.
Conclusion
HFH patients are more aggressively treated, have fewer cardiovascular risk factors and perform exercise and diet in a high percentage. HFC patients are frequently underdiagnosed and undertreated, have high frequency of cardiovascular risk factors and perform changes in lifestyle infrequently.

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P185

Bariatric surgery effects in lipids levels

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Aim
To analyze the influence of bariatric surgery over serum lipids in patients with morbid obesity after 1 year of surgery.
Methods
Retrospective study of 88 patients before and after 1 year of bariatric surgery (65 by pass and 23 sleeve). We collected data about age, sex, other diseases, anthropometric measures and biochemical parameters: glucose, uric acid, total cholesterol (TC), HDL-C, LDL-C, triglycerides (TG), VLDL and non-HDL-C, homocistein and leptin.
Results
Mean age: 45.11±10.01 years, 78.4% women. Weight pre and postsurgery: by pass 136.2±23.5 vs 87.1±14.7 ($P<0.05$) and sleeve 149.2±35.5 vs 96.3±21.1 ($P<0.05$). Mean weight lost for by pass was: 51.8±18.1 vs 52.7±24.1 kg in sleeve (NS). One year postsurgery there was a significant decrease of glucose, HbA1c, uric acid and leptin. There was a significant improvement in HDL-C: 43.9 9.2 pre vs 52.02 12.3 mg/dl postsurgery ($P<0.05$) and decrease of TC: 200.8±36.6 pre vs 185±35.9 mg/dl postsurgery ($P<0.05$), LDL-C: 128.9±31.9 pre vs 114.1±34.8 mg/dl postsurgery, TG: 150.5±81.1 pre vs 98.8±51.3 mg/dl postsurgery ($P<0.05$), C no HDL: 156.2±35.1 pre vs 133.8±38.8 postsurgery ($P<0.05$), VLDL: 30.1±16.2 pre vs 19.7±10.3 postsurgery ($P<0.05$). Mean

lipids levels before by pass and sleeve were (mg/dl): CT: 202±37.9 vs 199.2±28.2 (NS), HDL: 45.0±9.3 vs 43.8±10.3 (NS), TG: 150.8±82.7 vs 145.9±67.2 (NS), LDL-C: 131.2±33.5 vs 125.8±25.2 (NS), non-HDL-C: 156.9±38.1 vs 155.4±29.4 (NS), VLDL-C: 30.2±8.3 vs 29.2±10.2 (NS). Mean lipids levels 1 year after surgery were in by pass and sleeve (mg/dl): TC: 181.6±34.4 vs 194.1±44.6 (NS), HDL: 51.7±11.5 vs 53.4±14.7 (NS), LDL: 110.6±31.9 vs 131.0±41.2 ($P<0.05$), TG: 99.7±53.2 vs 78.7±28.6 (NS), non-HDL-C: 129, 8.9±32.1 vs 140.6±21.5 (NS), VLDL-C: 19.9±10.1 vs 15.7±9.6 (NS). Mean LDL-C decrease after by pass was 21.6±34.3 mg/dl vs an increase of 6.7±26.7 mg/dl ($P>0.05$) after sleeve. Mean decrease of non-HDL-C after by pass was 27.5±36.6 and after sleeve 7.2±26.5 ($P<0.05$). There was no correlation between weight and lipids decrease in both groups.
Before surgery 36.8% of patients were treated with lipid lowering drugs but 1 year after surgery only 6.8% were treated with these drugs.
Conclusion
Both methods of bariatric surgery improve lipid profile but patients with by pass surgery have more decrease of LDL-C and non-HDL-C than sleeve patients.

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P186

Prevalence of hyperandrogenism and polycystic ovary syndrome in female to male transsexuals

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Prevalence of hyperandrogenism (HA) and polycystic ovary syndrome (PCOS) in female to male transsexuals (FMT) is controversial. To known the prevalence of hyperandrogenism and PCOS in FMT, and their relation with insulin resistance (IR) and other cardiovascular risk factors (CVRF), we studied 77 Spanish consecutive FMT cases, the first ones who appeared in our Gender Unit between May 2007 and Dec 2008, aged 18–43 years. The subjects had never received hormonal treatment or sex reassignment surgery. Physical examination, ovary ultrasound, anthropometric measures, and metabolic and endocrine parameters were determined. Later the values obtained were compared according to the presence or absence of PCOS (Rotterdam 2003 criteria). Insulin resistance was determined using the homeostasis model assessment of insulin resistance (HOMA). The prevalence of HA was 49.4%, and those of PCOS was 36.4%, with IR in 27.6%, obesity in 19.5% and central obesity in 29.3%. In this population the prevalence of metabolic syndrome was 38.4% with ATP III criteria. Hyperandrogenemia was not only significantly related to obesity and other markers of IR but also with classic and emergent CVRF. In conclusion, FMT patients have a high prevalence of HA and PCOS, and with several CVRF. In FMT patients, the best marker of biochemical HA is the free androgen index.

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P187

Metabolic outcomes in childhood cancer survivors

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Aim
The aim of this study was to evaluate metabolic abnormalities in young adults getting treatments of acute lymphoblastic leukemia (ALL) and brain tumors (BT) in their childhood.
Methods
We examined 50 patients in two groups. The group-1: 18 ALL-survivors (nine women and nine men). All of them received cranial irradiation in dose up to 18 Gy and chemotherapy. In group-2: 32 BT-survivors (14 women and 18 men) were included. All patients received craniospinal irradiation up to 36 Gy and boost to the tumor up to 55 Gy and chemotherapy. The median age was 20.5 (19;23) and 20 (18;22) age at the time of treatment – 7.5 (5;9) and 12 (9;15), follow-up period was 13 years (12;16) and 5 years (2;10) respectively. Metabolic profile was examined.
Results
In the 1st group: four patients had dyslipidemia: elevation of LDL-C ($n=2$) and TG ($n=2$). OGTT was performed in 12 patients, one woman had FPG=6.2 mmol/l in combination with obesity (BMI=49.1 kg/m^2). Three patients had obesity. HOMA-index >2.5 was in seven patients. The age at the time of observation was negatively correlated with GH ($r=-0.723114$, $P=0.007872$). There were no significant differences in level of metabolic parameters between two groups.
In the 2nd group: we registered elevation of LDL-C (>3.4 mmol/l) in seven patients, both LDL-C and triglycerides (TG) (>1.2 mmol/l) in six. 12 of them had GH-deficiency, diagnosed with insulin tolerance test. OGTT was performed in 13 patients: FPG=6.1 mmol/l was found in one patient. The median of BMI – 19 (17;21.8). The BMI correlated with TG ($r=0.4$, $P=0.02$).
Conclusions
In ALL survivors elevated level of LDL-C and TG was diagnosed in 11.1%. 16% ALL survivors had obesity. BT survivors showed elevated level of LDL-C in 22.5%, increased of LDL-C and TG in 19.4%. There were no abnormalities in carbohydrate metabolism.

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P188

The associations between parathyroid hormone level and coronary artery diseases in subjects without significant renal dysfunction

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Introduction
Elevated parathyroid hormone (PTH) levels are associated with increased cardiovascular diseases (CVD) in the patients with impaired kidney function. We aimed to investigate whether PTH levels are associated with CVD in persons without significant renal diseases.
Methods
This is a cross-sectional study and we included 1951 Korean subjects aged ≥30 years (men 46.6%), who underwent 64-slice multidetector-row cardiac computed tomography (MDCT) to evaluate subclinical coronary artery disease. Anthropometric and biochemical parameters including intact PTH and 25-hydroxyvitamin D levels were measured. The study subjects were classified into three groups by tertiles of PTH levels (≤26, 26–38, and >38 pg/ml). The coronary artery calcium score (CACS), coronary artery stenosis, and multivessel involvement (≥2 vessels among major three coronary arteries) were assessed with MDCT.
Results
The PTH levels showed positive association with CACS after adjusting for cardiovascular risk factors and 25-hydroxyvitamin D ($R=0.293$, $P<0.001$). The prevalence of significant coronary artery stenosis (≥50%) were 6.4, 13.6, and 20.0% ($P<0.001$) and mutlivessel involvement were 1.2, 3.7, and 4.3% ($P<0.001$) according to the PTH tertiles. After adjusting for same cardiovascular risk factors, odds ratios (ORs) of significant coronary artery stenosis were 2.12 (95% CI 1.41–3.19) in the second tertile and 2.96 (1.99–4.39) in the third tertile of PTH. Regarding the multivessel involvement, the adjusted ORs were 2.66 (1.14–6.19) in the second tertile and 2.61 (1.12–6.07) in the third tertile of PTH compared to the first tertile of PTH. These positive associations were observed both in vitamin D sufficient (25-hydroxyvitamin D ≥20 ng/ml) and deficient (25-hydroxyvitamin D <20 ng/ml) groups.
Conclusion
Our results indicate that PTH level is an independent risk factor for CVD in the subjects without renal impairment and it affects the severity of diseases regardless of vitamin D status.

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P189

Serum cholesterol concentration and prevalence, awareness, treatment, and control of high LDL cholesterol in the Korea National Health and Nutrition Examination Surveys 2008–2010

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Introduction
The mortality rate from cardiovascular disease (CVD) among young adults has declined less than that in the older population, raising concerns about the increasing prevalence of obesity-related conditions including hypercholesterolemia in the younger population. We investigated the age-standardized mean levels of serum cholesterols and the prevalence, awareness, treatment and control rates of hyper-LDL-cholesterolemia based on age.
Methods
Nationally representative samples of 19 489 subjects aged $\geq$20 years were analyzed from the Korea National Health and Nutrition Examination Surveys 2008–2010. Hyper-LDL-cholesterolemia was individually evaluated by the 2004 National Cholesterol Education Program Adult Treatment Panel III guidelines.
Results
Age-standardized mean levels of total cholesterol, HDL-C, LDL-C and triglycerides were 186.8, 48.0, 112.9, and 136.0 mg/dl respectively. Age-standardized prevalence of hyper-LDL-cholesterolemia was 23.2% (men, 25.5% and women, 21.8%). Among subjects with hyper-LDL-cholesterolemia, awareness and treatment rates were significantly lower in younger adults ($<$50 years) compared to older adults $\geq$50 years (awareness, 8.0 vs 21.5%; treatment, 5.1 vs 18.5%, all $P<0.001$), indicating significant discrepancies in awareness and treatment rates of hypercholesterolemia between younger and older adults. Among subjects aware of their hyper-LDL-cholesterolemia, younger adults were more likely to have controlled LDL-C than the elderly (82.1 vs 67.5%, $P<0.001$).
Conclusions
Compared to the elderly, significant proportions of young and middle-aged adults are unaware of their hypercholesterolemia and are not treated with proper lipid-lowering medications. Early screening, education and proper management should be stressed in national public healthcare policies to reduce the increasing burden of CVD in the younger population with undiagnosed hypercholesterolemia.

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P190

Anomalies of the lipid balance in hypothyroidism: comparative study by sex

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Introduction
The thyroid hypofunction is at origin of lipid metabolism disorder that enhances cardiovascular risk and increases morbidity and mortality.
Objective
Search for lipid disorders in hypothyroidism comparing the results between the two sexes.
Population and Method
Retrospective study of 72 patients (54 F and 18 H), mean age of 55.63 years (53.66 F and 61.5 H) hospitalized between 1996 and 2012 for primary hypothyroidism. Only patients who underwent a metabolic evaluation were selected. All patients underwent a complete clinical examination, a thyroid function tests (hormonal and imaging) and metabolic exploration.
Results
Dyslipidemia was found in 77.4% of patients. It is more common in women: W (83.33%) vs M (57%) ($P<0.01$) regardless of its type. High cholesterol is the most common: 65.51% of cases: 69.5% W vs 50% M ($P<0.01$). Low HDL found in 52.63% of cases was noted only in women. Hypertriglyceridemia was the least frequent abnormality (35.7%) affecting 42.2% F vs 14.2% H ($P<0.01$). BMI and TSH means women were higher than men: 32.94 ± 7.6 vs 25.72 ± 3.44 kg/m^2 VS ($P<0.01$) and 100.6 ± 1.2 vs 61.26 ± 1.4 ($P<0.01$) for TSH.
Discussion
In agreement with the literature, lipid disorders are very common in hypothyroidism and its association with atherosclerosis is more severe than in the euthyroidism. The hypercholesterolemia is due to an increase in LDL receptor and a decrease in macrophage activity. In severe cases increased TG is secondary to decreased activity of lipoproteinelipase. This is a lipid atherogenic profile. It should be systematically sought and reassessed after opotherapy. The predominance of abnormalities in women can be explained by a higher BMI and TSH.

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P191

The pericarditis in the hypothyroidism

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Introduction
Pericarditis includes all inflammatory affections of the serous covering of the heart. The clinical expression and etiology of these disorders are highly variable. Of these, hypothyroidism is an important issue to recognize.
Objective
Find the frequency of pericardial effusion in primary hypothyroidism and appreciate its clinical and evolutionary characteristics.
Population and method
A retrospective study in 72 patients (54 W and 18 M), mean age 55.63 years (53.66 W, 61.5 M) hospitalized between 1996 and 2013 for primary hypothyroidism. Only patients who underwent cardiovascular assessment were selected. All patients underwent clinical examination, thyroid function, metabolic and cardiovascular exploration (chest radiography, cardiac electogram, cardiac Doppler). After replacement opotherapy, patients were reassessed.
Results
Pericardial effusion was found in 27.7%. It is small in abundance in 97.3%. One very important event effusion was observed. Pericarditis was frequently asymptomatic, discovered during the assessment of impact including in cases of great abundance. In 38.5% of cases moderate symptoms (precordialgia and dyspnea) were observed. Electrocardiographic disorders (diffuse microvoltage and repolarisation disorders) were observed in 80% of patients. Pericarditis was associated with hypertension in 50% of cases. The disappearance of the effusion and normalization of the cardiac electogram were observed in all patients after 3 months of opotherapy.
Discussion
Cardiovascular manifestations are often hidden and constants. They must be sought systematically because they have a significance prognostic. Pericardial effusion is found in one third of cases. It is usually asymptomatic. Major effusions are exceptional. Diastolic hypertension is described in 10–20% of women with hypothyroidism. Blood volume is decreased due to hypometabolism but peripheral vascular resistances are increased.

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P192

Vascular calcification: differences between atherosclerotic changes and media sclerosis? A pilot study

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Background
Calcification occurs physiologically in bone and pathophysiologically in the vasculature. Cardiovascular diseases are among the most common causes of death within patients with chronic kidney disease and crucial for kidney transplantation (RTX) outcomes.
Methods and aim
We investigated the pattern and the onset of expression of regulators of calcification (RC) in the arteria iliaca externa in 26 donors (D) and 25 recipients (R) of RTX to identify differences between atherosclerosis (AS) and media sclerosis (MS), suggesting specific differences in these patient groups.

Gene expression of RC was performed using TaqMan gene expression assays with a LC480 system. Determination of calcification type in donors (AS) was done histologically; in recipients (MS) via computed tomography (CT) by applying a score ranging from 0 to 3 in 0.5 intervals. Classification of stages in donors and recipients: 0 (no calcification of vessels), 1 (AS: intima thickening, MS: CT score 0.5), 2 (AS: intima calcification, MS: CT scores 1–3).
Results
Gene expression of OPG, OPN, RANKL, SMAD6, RunX2 and BSP was significantly higher in donors than in recipients ($P=0.004$, 0.001, 0.004, 0.026, 0.027 and 0.068 respectively).
But gene expression did not significantly differ in unaffected D and R at stage 0. In early stages of AS, OPG expression increased, whereas expression in early MS was unchanged. In progressive calcification, expression of OPG, OPN and SMAD6 was significantly higher ($P=0.048$, 0.024, 0.048 respectively) in D (AS) than in R (MS); and of RANKL and RunX2 ($P=0.089$, 0.085 respectively) only borderline higher. AS and MS were compared separately.
Conclusion
We were able to demonstrate a different gene expression pattern in AS and MS and a different onset of calcification. This supports a more comprehensive insight in calcification mechanisms.

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P193

Apelin as a marker of an insulin resistance in patients with essential hypertension

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Aim of investigation was to estimate a serum level of apelin in patients (pts) with essential hypertension and insulin resistance.
Methods
94 patients with EH were examined. Carbohydrate and lipid metabolisms were investigated. Apelin's blood levels were estimated by ELISA 'Phoenix', USA. Insuline resistance (IR) criteria was insulin level more than 12.2 mkU/ml. Data is present as median (Q25 and Q75). FINDRISK questionnaire was used to estimate risk of type 2 diabetes development.
Results
IR was estimated in 60.0% pts with EH. Pts were divided into two groups according fasting insulin level: 1 gr. – 57 pts with EH and IR (age – 58.0 (51.5; 65.0), 21 males, 36 females); 2 gr. – 37 pts with EH without IR (age – 59.5 (49.0; 63.0), 19 males, 18 females). Apelin's activity was higher in pts with EH (0.24 (0.15; 0.46) ng/ml comparing with control group 0.13 (0.12; 0.17) ng/ml, $P<0.001$). In pts of 1 gr. apelin was significantly higher – 0.32 (0.14; 0.44) ng/ml than in pts of 2 gr. 0.23 (0.16; 0.43) ng/ml, <0.05. Apelin correlates with IR index ($r=-0.38$; <0.05) and fasting insulin ($r=0.49$; <0.05). In pts of 2 gr. apelin correlates with Hb_{A1c} ($r=0.52<0.05$). Findrisk questionnaire results showed increased risk of T2D development in pts of 1 gr. (12.5 (9.0; 15.0) vs 9.0 (8.0; 13.0), <0.05).
Conclusion
IR was estimated in 60.0% pts with EH and was accompanied by overexpression of apelin, increased risk of type 2 diabetes development, pronounced changes in lipids and high atherogenic index. It's possible to use apelin activity as a marker of insulin resistance in patients with essential hypertension.

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P194

Insulin dynamics and its associated signalling pathways in equids predisposed to laminitis

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Laminitis, an inflammatory condition of the sensitive and specialised architecture (the laminae) in the equine hoof, can be induced by over-ingestion of non-structural carbohydrates (NSC) from spring/summer pasture. Some equids that are predisposed to laminitis appear to share characteristics described in human patients with metabolic syndrome, such as vascular dysfunction, obesity, development of an inflammatory profile and insulin resistance. We investigated whether adipose tissue from laminitis prone equids (LP) functions differently from non-laminitis prone equids (NL), by examining gene expression (using a 44K equine expression microarray) in subcutaneous adipose tissue from healthy LP and NL ($n=6$ each group), obtained at two different times of the year (season: summer and winter) and following increased NSC consumption (dietary intervention: 7 days in the winter). Data were first analysed in GeneSpring and then the expression of 40 genes associated with insulin signalling compared between groups using a linear mixed model in SPSS statistics 20. Genes with a >1.5-fold difference and $P<0.05$ were considered significant. In addition, an oral glucose tolerance test (OGTT) was performed on each occasion. LP always had a significantly ($P<0.05$) increased insulin response to oral glucose (area under curve (AUCi)) compared to NL. After dietary intervention, AUCi was significantly increased in NL ($P<0.05$), but unchanged in LP. AKT3 and CBL were upregulated in LP compared to NL in the summer, whilst HK2 and INSL3 were downregulated. DOK2 and CBL (LP), INSL3 and PPP1CA (NL) were upregulated whilst INSR and IRS2 (NL and LP) were downregulated in summer compared with winter. SLC2A1 (LP) and FRS3 (NL) were upregulated by dietary intervention. An increase in secretion of insulin in LP was associated with a concurrent regulation of genes within the insulin signalling pathway. Short-term dietary intervention did not induce the same changes in insulin dynamics as did season.

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P195

Laminitis: finding the key to predisposition of the metabolic disorder affecting the hoof in equids

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Laminitis, an inflammatory condition of the sensitive and specialised architecture (the laminae) in the equine hoof, can be induced by over-ingestion of non-structural carbohydrates (NSC) from spring/summer pasture. Some equids that are predisposed to laminitis appear to share characteristics described in human patients with metabolic syndrome. We investigated if adipose tissue from laminitis prone equids (LP) functions differently from non-laminitis prone equids (NL), by examining gene expression in subcutaneous adipose tissue from healthy LP and NL ($n=6$ each group), obtained in the summer and winter (season) and following increased NSC consumption (dietary intervention: 7 days in the winter). Genes and signalling pathways that differed between group and season/dietary intervention were compared using a 44K equine expression microarray. Data were analysed in GeneSpring and Ingenuity Pathway Analysis. Genes with greater than twofold, $P<0.01$ were considered significant. The most significant differences in global gene expression were observed between summer and winter, with 244 and 174 genes differentially expressed in the NL and LP respectively. The LP and NL groups showed significant differences between groups in the summer (141 genes), whereas the two groups were more similar in the winter (40 genes significantly different) when laminitis is uncommon. Eight of the top ten upregulated molecules and three of the top five canonical pathways that differed between LP and NL in the summer were associated with inflammation and/or immunity. There were significantly fewer changes in gene expression following dietary intervention (27 and 44 genes in PL and NL respectively), and only 23 genes differed between the groups after dietary intervention. LP ponies appear to have a different adipose tissue profile to NL, particularly in the summer. Inflammatory genes and pathways were significantly over-represented in the LP group suggesting higher baseline levels of inflammation or priming of inflammatory pathways may contribute to a predisposition to laminitis.

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Fetuin-A as a marker of cardiovascular risk in patients with type 2 diabetes

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Introduction
It is known that type 2 diabetes increases the risk of cardiovascular disease. Fetuin-A is a multifunctional serum glycoprotein and its role in the pathogenesis of type 2 diabetes, atherosclerosis and cardiovascular disease is still discussed.
Material and methods
The study was conducted in 36 patients (12 F and 24 M) with type 2 diabetes mellitus (DM2) and acute coronary syndrome (ACS), aged mean 70.22±7.62. The group was divided into subgroups: 26 subjects with myocardial infarction (MI) and ten subjects with unstable angina (UA) as well as nine subjects with uncomplicated course of ACS and 27 subjects with complications including cardiac arrhythmias, pulmonary oedema, cardiac arrerst. The control group was composed of 17 patients (6 F and 11 M) with type 2 diabetes and without cardiovascular disease aged mean 56.06±11.77. Determinations of serum fetuin-A levels with the use of Human Fetuin-A ELISA Kit (an assay sensitivity of 3.5 μg/ml) were performed. For statistical analysis, Statistica 8.0 StatSoft was used (Mann–Whitney *U* test and Spearman's test were applied).
Results
Patients with DM2 and ACS had decreased fetuin-A concentrations compared to subjects in control group (0.515±0.149 vs 0.608±0.153 g/l; $Z=1.984$; $P<0.05$). Subjects with DM2 and MI had lower fetuin-A levels than patients with DM2 and UA (0.483±0.147 vs 0.597±0.126 g/l; $Z=2.101$; $P<0.05$). The inverse statistically significant ($P=0.003$; 0.042; 0.039 respectively) correlations between fetuin-A concentration and troponin, CK-MB and myoglobin levels, measured few hours after myocardial infarction, have been observed. Higher fetuin-A levels have been noted in subjects with DM2 and complications in the course of ACS compared to those without complications (0.547±0.143 vs 0.418±0.129 g/l; $Z=2.155$; $P<0.05$).
Conclusions
Fetuin-A concentration is decreased in patients with diabetes and acute coronary syndrome. It correlates negative with severity of myocardial ischemia as well. Fetuin-A deficiency may be a predictor of cardiovascular risk and a marker of ischemia's severity in patients with type 2 diabetes.

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P197

Osteoprotegerin as a marker of myocardial damage in patients with type 2 diabetes and acute coronary syndrome

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Introduction
It's known that type 2 diabetes increases the risk of cardiovascular disease. Silent myocardial ischemia occurs frequently in diabetics and may result in more severe coronary artery disease. Osteoprotegerin (OPG) is a glycoprotein secreted mainly by osteoblasts but it's also produced by heart muscle. Its role in the pathogenesis of type 2 diabetes, atherosclerosis and future cardiovascular events is still discussed.
Material and methods
The study was conducted in 36 patients (12 F and 24 M) with type 2 diabetes and acute coronary syndrome aged mean 70.22±7.62. In the studied group, the average concentration of OPG was 7.283±3.516 pmol/l. The group was divided into subgroups: 26 subjects with myocardial infarction (MI) – 13 patients with ST elevation (STEMI-MI) and 13 patients with non-ST elevation (NSTEMI-MI) as well as ten subjects with unstable angina (UA). Determinations of serum osteoprotegerin levels with the use of MicroVueTM OPG-EIA (an assay sensitivity of 0.4 pmol/l) were performed. For statistical analysis, Statistica 8.0 StatSoft was used (Mann–Whitney *U* test and Spearman's test were applied).
Results
Patients with MI had increased OPG concentrations compared to subjects with UA (8.244±3.639 vs 4.782±1.292 pmol/l; $Z=2.807$; $P<0.05$). In the group of patients with MI, subjects with NSTEMI-MI had higher OPG levels than patients with STEMI-MI (9.702±4.069 vs 6.786±2.534 pmol/l; $Z=2.105$; $P<0.05$). What's more, the positive statistically significant ($P=0.003$; 0.004; 0.006 respectively) correlations between OPG concentration and troponin, CK-MB and myoglobin levels, measured few hours after MI, have been observed. No statistically signicant difference between patients with MI and Q waves and without Q waves have been noted.
Conclusions
OPG concentration is increased in diabetics with MI and subjects with NSTEMI-MI. It correlates positively with severity of myocardial ischemia as well. OPG may be a risk factor for the progression of atherosclerosis and onset of cardiovascular disease and predict cardiovascular events in diabetic patients.

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P198

Epigenetic control of renin–angiotensin–aldosterone system in hypertrophic heart

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The activation of local renin-angiotensin-aldosterone system (RAAS) plays a pivotal role in the overall pathophysiology of the cardiovascular diseases. We have reported increased mRNA levels of angiotensinogen, angiotensin converting enzyme (ACE) and CYP11B2 (aldosterone synthase gene) in the heart of salt-sensitive hypertensive rats complicated with cardiac hypertrophy. However, the mechanism of control of gene expression of each component of RAAS gene in the heart is unknown. We analyzed epigenomic alteration, which controls the CYP11B2 in the human heart (cardiomyopathy, $n=9$; non-cardiomyopathy, $n=6$). CpG dinucleotides in the CYP11B2 promoter were found to be hypermethylated in tissues with low expression, but not in those with high expression, of CYP11B2. Methylation of the CYP11B2 promoter fused to a reporter gene decreased transcriptional activity. CYP11B2 mRNA levels were inversely correlated with CYP11B2 methylation in human myocardium, and increased CYP11B2 mRNA levels were associated with CYP11B2 demethylation in the hypertrophic heart. CpG dinucleotides in the angiotensinogen gene promoter were also found to be hypermethylated in tissues with low expression. Hypertrophic hearts induced by high salt intake showed hypomethylated state of angiotensinogen gene. Advances in understanding of epigenetic modifications of tissue RAAS in the progression of cardiac hypertrophy and heart failure could be of great significance in predicting the pace of disease progression, developing targeted therapeutic strategies in preventing the progression of cardiovascular diseases.

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P199

Occurrence of hipothyreosis in patients with metabolic syndrome

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Metabolic syndrome is an important social problem concerning a growing number of people. In different countries across Europe, its incidence is estimated at 17.4–28%. The metabolic syndrome is a constellation of risk factors for cardiovascular diseases. Hipothyreosis can additionally influence on lipid and carbohydrate disorders.
The described study was a prospective, two-centre (A. Jurasz University Hospital No. 1 in Bydgoszcz, District Hospital in Wabrzezno, Poland) screening study of 12-month duration. The study participants were 147 patients (120 women, 27 men, aged 28–95) with metabolic syndrome diagnosed according to the 2005 IDF.
The group was divided into two subgroups: with hipothyreosis ($n=59$) and with euthyreosis ($n=88$). We observed differences between the average level of triglycerides in control and study' groups (161.46 vs 134.8 mg/dl; $P=0.047$). Also we noticed statistically significant differences between the average level of impaired fasting glucose in control and study' groups (112.33 vs 126.07 mg/dl; $P=0.044$). There were no substantial differences in other parameters.
We suggest that patients with metabolic syndrome should have marked TSH and patients with hipothyreosis should be monitoring toward pronouncement of metabolic syndrome in the future.

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P200

Flexibility of ectopic lipids in physically active, healthy individuals

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Introduction
Ectopic lipids are fuel stores in non-adipose tissues (i.e. skeletal muscle (IMCL), liver (IHCL), heart (ICCL)). An aerobic-exercise bout leads to a decrease in IMCL ('working tissues'), whereas it is not established whether a single but of exercise influences IHCL or ICCL.
Increased IMCL and IHCL have been related to impaired insulin action in skeletal muscle and liver. It is hypothesized that fat availability (subcutaneous and visceral fat mass), exercise capacity (VO_{2max}) and insulin sensitivity influences the exercise-induced changes in ectopic lipids.
Methods
10 male, physically active subjects (age: 28.9±6.4 years; VO_{2max}: 56.3±6.4 ml/kg per min, BMI: 22.75±1.4 kg/m^2) were recruited. VO_{2max} was assessed using spiroergometry, insulin sensitivity by HOMA-index. Visceral and subcutaneous fat mass were separately quantified by MRI. IMCL, IHCL and ICCL were measured using ^{1}H-MR-spectroscopy before and after a 2 h-exercise at 50–60% of VO_{2max}. In a subgroup of five subjects, a third ectopic lipid assessment was performed a day after the 2 h-exercise test.
Results
A 2 h-exercise resulted in a significant decrease from baseline in IMCL (−17±22%, $P=0.008$), ICCL (−17±14%, $P=0.002$) and an increase in IHCL (42±29%, $P=0.004$). No significant correlations were found between the respective changes in ectopic lipids and measures of fat availability, exercise capacity or insulin sensitivity. MR-spectroscopy a day after exercise showed an re-increase of IMCL and ICCL still below pre-exercise values (IMCL: −3% ($P=0.6$), ICCL: −22% ($P<0.05$). In contrast, IHCL decreased to a level that was not significantly different to the pre-exercise level.
Conclusions
i) In healthy subjects all ectopic lipids are flexible fuel stores that are influenced by physical exercise, albeit in different directions with a decrease in myocardium and skeletal muscle ('working tissues') and an increase in liver ('storage tissue').
ii) Preliminary data suggest that this is a transitory phenomenon.

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P201

Low testosterone syndrome protects from major adverse cardiovascular events in subjects at high cardiovascular burden

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Introduction
The role of testosterone in cardiovascular (CV) health of men is controversial. Several data suggest that hypogonadism is associated with CV mortality but not morbidity. However, recent evidence shows that hypogonadal subjects treated with testosterone replacement therapy have a higher incidence of major adverse CV events (MACE). The aim of this study is to analyse whether the gonadal status might predict MACE incidence according to the previous history of MACE, in a cohort of subjects complaining for sexual dysfunction.
Methods
A consecutive series of 1687 patients was followed-up for a mean time of 4.3±2.6 years for new occurrence of MACE, detecting 139 events.
Results
Hypogonadism (total testosterone <12 nmol/l) was not associated with an increased incidence of MACE in the entire cohort. However, when considering patients with a previous history of MACE, hypogonadism was associated with a reduced risk of MACE, even after adjusting for confounders (HR=0.498 (0.240; 0.996); $P=0.049$), whereas no relationship was observed in subjects free of previous MACE. Similar results were observed when reduced testis volume (TV) was considered as a predictor of MACE in subjects with previous MACE (HR=0.486 (0.257; 0.920); $P=0.027$). In patients with a history of MACE, but not in those free of MACE, having both low testosterone and low TV was associated with a higher incidence of MACE as compared with subjects with only one or none of these conditions, even after adjusting for confounders (HR=0.514 (0.306; 0.864); P for trend <0.02). Notably, CV risk estimated with risk engines based on traditional risk factors was not different between hypogonadal and eugonadal subjects.
Conclusions
Present data show that hypogonadism could be interpreted as a protective mechanism in unhealthy conditions, such as a previous MACE, to avoid fatherhood and spare energy.

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P202

Serum homocysteine levels are decreased in levothyroxine-treated women with autoimmune thyroiditis

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Introduction
Some studies suggest that thyroid autoimmunity might be associated with increased cardiovascular-risk. However, the exact pathophysiology of this relationship has not yet been fully understood. In this study we aimed to analyze the influence of the levothyroixine ($L\text{-}T_4$) replacement therapy and of anti-thyroperoxidase antibodies (TPOAbs) on homocysteine (Hcy) levels in patients with thyroid autoimmune disease.
Methods
31 euthyroid women with Hashimoto is thyroiditis (HT) treated with $L\text{-}T_4$ and 26 euthyroid women with positive TPOAbs, non-treated with $L\text{-}T_4$ (non-treated HT) were enrolled to this case–control study. 40 healthy women matched for age and BMI served as controls. Exclusion criteria included: a history of any acute or chronic disease, such as diabetes mellitus, hypertension, angina pectoris, evidence of any kidney or liver disorder, use of any medications (including oral contraceptives and vitamin supplements), smoking, alcoholism.
Results
TPOAbs titers were significantly higher in both groups of patients with thyroid autoimmune disease (treated and non-treated HT) in comparison to healthy controls. Hcy levels were significantly lower in treated HT patients (Me 11 μmol; IQR 4.2 μmol) as compared with healthy controls (Me 13.35 μmol; IQR 6.34 μmol; $P=0.0179$). In contrast, there was no difference in Hcy levels between non treated HT and control group in Hcy. Levels of TSH, FT_4, TC, LDL, HDL, and TAG did not differ between the study groups and the control group.
Conclusion
LT-4 replacement therapy is associated with a decrease of Hcy levels in patients with HT.

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P203

ARR screening using IDS-iSYS aldosterone and direct renin: effects of medication in essential and renovascular hypertension, Cushing's syndrome and primary aldosteronism

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Background
Identifying hypertensive patients with primary aldosteronism (PA) using the aldosterone to renin ratio (ARR) is crucial for optimizing their treatment. Various medications used to treat hypertension are known to alter levels of aldosterone and renin, thus affecting the ARR. As withdrawing all medication before screening is often unrealistic, we aimed to determine the degree of interference of some commonly used agents on the ARR using assays on the automated IDS-iSYS platform (Boldon, UK).
Methods
We investigated a cohort of 65 patients (32 males and 33 females) with essential hypertension (EH), renovascular hypertension, PA or Cushing's syndrome. Fifty-seven of the patients were taking anti-hypertensive medication at the time of

screening. Mean age was 59 ± 17 years. For the majority of patients, both supine and standing samples were available. We used IDS-iSYS aldosterone and direct renin assays to measure the ARR for each sample. A previously determined ARR cut-off of >1.1 ng/dl per μU per ml was used to indicate the presence of PA.
Results
In patients with PA, 15 of 19 samples had an ARR value above the cut-off. All samples from patients with renovascular hypertension ($n=16$) and Cushing's ($n=3$) displayed a negative ARR regardless of medication. In samples from patients with EH ($n=78$), 20 false positive ARRs were measured, 16 of which were standing samples. Seventeen of the 20 samples were from patients taking β-blockers, whereas two were from patients not taking any hypertension medication.
Conclusions
Interrupting hypertension medication for ARR screening gives the most accuracy but is not ideal for the patient. We observed a false positive outcome in 26% of samples from patients with EH, which was mostly associated with β-blockers and/or standing sampling position. Therefore, it may not be necessary to withdraw all drugs for the ARR screening as long as the effects are taken into account when interpreting results.

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P204

eNOS, p22 phox, CETP and ERα gene polymorphisms related to metabolic–endocrine parameters in postmenopausal women with metabolic syndrome: a population based study

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Objective
We previously found an association between eNOS(G894T) polymorphism and components of metabolic syndrome (MetS); thus, we investigated the metabolic–endocrine changes in postmenopausal women with incipient MetS and the interaction with the polymorphisms of eNOS-G894T, p22phox-930 A/G, CETP TaqIB and ESR1 (PvuII and XbaI) genes.
Methods
postmenopausal women aged between 60 and 80 years from a population-based study were classified into the two groups, non-MetS (212) and incipient MetS (68). Clinical, anthropometric and endocrine–metabolic parameters were measured. A total of five single nucleotide polymorphisms were determined and tested for interacting with these parameters.
Results
The weight, waist circumference, blood pressure, WBC, uric acid, LDL-C, apolipoprotein B, triglycerides, fasting glucose, insulin, HOMA-IR, TC:HDL-C ratio, apoB:apoA-I ratio were higher in MetS group ($P<0.02$). The significant high levels of E_2, T_3, GHBP, PTH, E_2:E_1 ratio and low levels of cortisol, SHBG, FSH, LH, IGFBP1, cortisol:DHEA ratio were also evaluated in MetS group. Most of biochemical variables are normal range in both groups except glucose, triglyceride, LDL-C, apo B that are in the high borderline range in MetS group. Testing of Hardy–Weinberg equilibrium in genetic association studies showed significant differences in allelic distribution of p22phox gene ($P=0.033$) and in distribution of *XbaI* ESR1 genotypes ($P=0.021$). Significant associations were detected between gene SNPs and metabolic–endocrine changes. In MetS group the carriers of TT (eNOS-G894T) genotype had higher levels of blood pressure, glucose ($P<0.02$), GG (p22phox A/G) had higher levels of BMI, VSH, apoB:apoA ratio ($P<0.03$), B2B2 (*CETP* B1/B2) had higher levels of TG, TG:C-HDL ratio ($P<0.03$). CC (*PvuII*) and GG (*XbaI*-ER1) genotypes showed higher levels of glucose ($P< 0.002$).
Conclusions
The results show an interaction between the studied polymorphisms and the endocrine-metabolic changes in MetS pathogenesis. The elevated values of TC:HDL-C and apoB:apoA-I ratios could be risk indicators for calculation cardiovascular risk of MetS.

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P205

Identification of 4 statin benefit groups according to NHLBI ATP IV criteria among Venezuelan women: EEM–lipid study

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The 2013 guideline (NHLBI ATP IV) on the treatment of blood cholesterol in adults was recently published. It focuses on identification of 4 Statin Benefit Groups (4SBG), in which the potential for Atherosclerotic Cardiovascular Disease (ASCVD) risk reduction benefit clearly exceeds the potential for adverse effects.
Objective
To estimate the prevalence of 4SBG among Venezuelan women and to determine its association with hypertension, BMI, waist circumference (WC), fasting blood glucose, age, obesity, reproductive history, socioeconomic status, and lifestyle.
Methods
In this cross-sectional study, a sample of 527 women (40–75 years old) was selected in gynecology clinics from 24 provinces of Venezuela. The levels of blood pressure, serum glucose, Col-T, HDLc, LDLc, and TG were measured for all them. 4SBG was defined according to ATP IV: i) clinical ASCVD; ii) LDLc ≥190 mg/dl; iii) diabetes and LDLc 70–189 mg/dl; iv) neither ASCVD nor diabetes, LDLc 70–189 mg/dl, estimated 10-year ASCVD risk ≥7.5% (by Pooled Cohort Equations).
Results
The prevalence (95% CI) of 4SBG, namely A, B, C, and D were 2.7 (1.2–4.0), 8.3 (6.0–10.7), 19.3 (16.5–22.6), and 8.0% (5.7–10.2) respectively. Overall, 61.5% (58.9–64.1) of women did not belong to 4SBG. WC was higher in A and C groups. Prevalences of HTA and obesity were higher in 4SBG than in non 4SBG women ($P<0.001$). The prevalence of 4SBG women increased steadily in line with age ($P<0.001$). Interestingly, the prevalence was 100% in the 70-year-old age or older Group.
Conclusions
EEM-Lipid Study data indicate that nearly 40% of the Venezuelan women (40–75 years old) would require the use of statins as recommended by NHLBI ATP IV. Furthermore, for all women over age 70 would be indicated using it. Therefore, effective public health education and urgent precautions are needed.

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P206

Alterations in ambulatory blood pressure monitoring are frequent and associated to cardiovascular risk factors in patients with type 1 diabetes

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Objectives
To evaluate the prevalence of blood pressure alterations by ABPM and its association with clinical factors in normotensive and normoalbuminuric patients with type 1 diabetes (TDM1).
Methods
Cross-sectional study including normotensive and normoalbuminuric patients with TDM1. Altered ABPM was considered when: i) Mean systolic pressure (sBP) was ≥130 mmHg in the 24 h and daytime periods and ≥120 mmHg in the night-time 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, and/or iii) nocturnal fall in either sBP or dBP was ≤10% (non-dippers).

Results
85 patients (55% women), aged 27.9±6.1 years with a disease duration of 12.3±6.5 years. 32% presented mean sBP or dBP altered during daytime period, 32% more than 50% of pathological readings during daytime and 41.6% were non-dippers. Altered ABPM was more prevalent in men. BMI was higher in patients with elevated sBP during daytime (26.4±3.4 vs 23.5±2.7 kg/m^2, *P*: 0.002) with significant correlation with 24 h sBP (*r*: 0.2, *P*: 0.01) and night-time sBP (*r*: 0.22, *P*: 0.04). Non dippers showed worse metabolic control since diagnosis (HbA1c 8.6±1.4 vs 7.9±1.4%, *P*: 0.04). HDL cholesterol level was lower and triglycerides level higher in subjects with altered sBP or dBP during daytime (HDLc: 55.9±14.4 vs 66.8±13.8 mg/dl, *P*: 0.03; TG 97.9±52.5 vs 65.7±13.5 mg/dl, *P*: 0.003). Significant correlation was detected between TG levels and daytime dBP (*r*:0.2, *P*: 0.01) and between HDLc and 24 h sBP (*r*: −0.22, *P*: 0.003) and night-time sBP (*r*: −0.22, *P*: 0.003).
Conclusion
Prevalence of altered ABPM is high in normoalbuminuric and normotensive TDM1. Altered BP was more frequent in men, in patients with elevated BMI, worse metabolic control and lipid profile. ABPM should be performed in patients with TDM1 and cardiovascular risk factors to detect undiagnosed BP alterations and to assess the convenience of treatment.

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P207

Flaccid penile acceleration as a marker of cardiovascular risk in men without classical risk factors

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Introduction
Conventional cardiovascular (CV) risk factors identify only half of subjects with incident major adverse CV events (MACE). Hence new markers are needed in high CV risk subjects, as those with erectile dysfunction (ED). A role for dynamic peak systolic velocity (D-PSV) at penile color Doppler ultrasound (PCDU) has been suggested, but it is operator-dependent and time-consuming. Flaccid penile acceleration (FPA) is a PCDU parameter that reflects PSV, the systolic rise time (SRT) and end diastolic velocity (EDV), arithmetically defined as (PSV−EDV)/SRT.
Aim
To verify, in a large series of ED patients, whether FPA has a role in predicting MACE.
Methods
A selected series of 1903 patients (aged 54.6±11.7) attending our outpatient clinic for ED was retrospectively studied from January 2000 until July 2012. A subset of this sample ($n=622$) was enrolled in a longitudinal study, ended in December 2007.
Main outcome measures
Several clinical, biochemical, and instrumental (PCDU) parameters were studied.
Results
Decreased FPA levels were associated with worse metabolic profile and sexual symptoms. In addition, FPA was positively associated with both total and calculated free testosterone. In the longitudinal study, unadjusted incidence of MACE was significantly associated with lower baseline FPA. When FPA was introduced in a multivariate model, along with D-PSV, after adjusting for age and chronic disease score, lower FPA, but not D-PSV, was associated with incident MACE in low risk – i.e. younger (HR=0.48 (0.23–0.99)), non hypertensive (HR=0.59 (0.38–0.92)), non obese (HR=0.68 (0.49–0.96)) or non diabetic (HR=0.67 (0.49–0.96) subjects; all $P<0.05$ – but not in high risk ones. FPA demonstrated a threshold effect in predicting MACE at a value <1.17 m/s$_2$ which showed a threefold increase in incidence of MACE in apparently low-risk individuals.
Conclusions
FPA is an easily obtained PCDU parameter and capable of identifying adverse metabolic and CV profiles, particularly in apparently low-risk individuals with ED.

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P208

Total and HDL-cholesterol are lower in lean PCOS women

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Aim
To assess lipid levels in patients with PCOS and normal body weight.
Materials and methods
139 patients admitted to the Gynaecologic Endocrinology Clinic of the Jagiellonian University's Collegium Medicum agreed to take part in this research, and PCOS, according to the Rotterdam criteria, was found in 96 of them. The control group consisted of 43 patients with FAI <5. All of the 96 patients had a normal (BMI <25) body weight. This index, as well as blood samples, were obtained during routine investigations at the hospital.
Results
No statistically relevant difference was found in LDL and triglyceride levels between patients with PCOS and the control group. Patients with PCOS had significantly lower HDL levels (1.68±0,38 vs 1.94±0.36; $P<0.01$) and total cholesterol levels (4.59±1.39 vs 5.05±0.86; $P<0.02$).
Conclusion
Because of the lower HDL levels in patients with PCOS, they suffer an increased risk of atherosclerosis.

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P209

LDL cholesterol is higher in overweight and obese PCOS women

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Aim
To assess lipid levels in patients with PCOS and BMI >25.
Materials and methods
102 patients admitted to the Gynaecologic Endocrinology Clinic of the Jagiellonian University's Collegium Medicum agreed to take part in this research, and PCOS, according to the Rotterdam criteria, was found in 87 of them. The control group consisted of 15 patients with FAI <5. All of the 87 patients had BMI >25. This index, as well as blood samples, were obtained during routine investigations at the hospital.
Results
No statistically relevant difference was found in total cholesterol levels, as well as in HDL and triglyceride levels, between patients with PCOS and the control group. Patients with PCOS had significantly higher LDL levels (2.96±0.73 vs 2.42±0.57; $P<0.02$).
Conclusion
Our results may suggest greater cardiovascular risk in overweight and obese PCOS women.

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Clinical case reports – Pituitary/Adrenal

P210

Diabetes insipidus and hypopituitarism in a patient with idiopathic pulmonary fibrosis

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Diabetes insipidus is a disease characterized by the inability to concentrate urine. The common form is central diabetes insipidus (CDI) caused by a lack of AVP after destruction of supraoptic–paraventricular nuclei. Further investigations are needed to establish its cause.
Case report
A 38-year-old woman presented with prompt polyuria–polydipsia. She has been taking contraceptive tablets for 2 years, smoked four to five cigarettes per day. Blood test dismissed osmotic polyuria, so she was admitted into hospital to carry a water deprivation test (compatible with CDI).

She stopped contraceptive therapy and despite normal pituitary study, amenorrhea persisted (FSH 5.26 μU/ml, LH 2.59 μU/ml, estradiol 15 pg/ml, and prolactin 7 ng/ml). Hormone replacement therapy was started.
Pituitary RMI showed partial agenesia of corpus callosum and microadenoma of 7 mm. CBC, plasmatic calcium, α-fetoprotein and βhcg were normal. LDH 193.00 IU/l and antipituitary antibodies negatives.
18 months after diagnosis she was referred with dyspnea. Radiography showed reticular infiltrates in upper lung lobes; normal respiratory tests. HR-CT evidenced 2 cm bilateral lung cysts on superior-media lobes. Normal bronchoscopy and BAL. Transbronchial biopsy inconclusive thoracoscopy and biopsy showed fibrosis with lymphocytic infiltrates (strange body reaction). No treatments were indicated but stop smoking.
Two years later she appeared with disturbance thyroid axis (TSH 0.87 μIU/ml, T_4 0.6 ng/dl) treated with levothyroxine 100 μg/day and also low IGF1 (71 ng/ml, age range 120–307), she initiated growth hormone replacement.
Additional tests ACE, ANA, ANCA, rheumatoid factor, protein account, abdominal ultrasound and bone map were all normal. PET–CT: lung parenchyma honeycombing.
Conclusion
Although she was initially diagnosed as idiopathic CDI, further studies made necessary differential diagnosis with other systemic diseases.
According to radiographic pattern and pituitary disease, etiologies to be considered are histiocytosis X (during scar phase, Langerhans cells may disappear in biopsy) and sarcoidosis (less likely).

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P211

Can bexarotene be a candidate drug for the medical therapy of Cushing's syndrome?

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We report a patient with mycosis fungoides treated with bexarotene (Targretin), a synthetic retinoid analog with specific affinity for retinoid X receptor. This patient developed hypopituitarism characterized by hypogonadism, hypothyroidism, and hypoadrenalism. Although central hypothyroidism is a common side effect of bexarotene, central hypogonadism, and hypoadrenalism has been reported in one case. Clinicians should have high index of suspicion for hypopituitarism in patients under bexarotene therapy. On the other hand, this side effect may be promising for the treatment of TSH-secreting pituitary tumours and Cushing's syndrome. In this regard we suggest that bexarotene should be evaluated as a potential therapy for Cushing's syndrome in which the available medical drugs have limited efficacy and potential side effects.

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P212

Familial 46, XY gonadal dysgenesis

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46, XY disorders of sex development are rare diseases secondary to gonadal dysgenesis (GD) and disorders of androgens synthesis or action. Familial forms of GD are very rare; we report here the observations of two siblings with 46, XY GD. The first patient whose parents were relatives, raised as a girl consulted at 3 years for ambiguous genitalia, at clinical exam we found a small phallus, partial fusion of labio-scrotal folds with one orifice at the phallic base and palpable gonads within the labio-scrotal structures. Pelvic ultrasound confirmed the presence of gonads; genitography found the presence of mullerian ducts derivatives, hormonal evaluation found low testosterone level with poor response to HCG stimulation, Barr body test was negative. The second sibling diagnosed during familial investigation was also reared as a girl; she was then aged 10 years. She had the same findings with ambiguous genitalia, presence of gonads in the inguinal canal, low testosterone level with poor response to HCG stimulation and a 46, XY karyotype. The two patients underwent bilateral gonadectomy in accordance with sex of rearing, and thereafter received estrogens treatment. Knowledge of familial forms of GD allows diagnosis of other affected siblings and genetic counsel to the family.

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P213

Comorbidity of gastrointestinal stromal tumor and pituitary macroadenoma in patient referred with gastrointestinal bleeding

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We report a case of GIST comorbidity with pituitary macroadenoma presenting with gastrointestinal bleeding.
Case
A 56-year-old male patient was admitted to the emergency department with complaints of hematemesis. Antral gastritis and a mass about 3 cm in diameter with irregular margins in the ampulla detected in upper gastrointestinal endoscopy. Irregular, heterogeneous, hypoechoic solid mass lesion, ~ 36× 48 mm in size, was observed inferior–lateral neighborhood of the pancreas in the upper abdomen ultrasonography. Solid mass lesion ~ 4 cm in diameter was observed under the head of the pancreas slightly distorting the duodenal ans detected in abdomen tomography. Whipple procedure, pancreatic resection and cholecystectomy was performed to the patient with an initial diagnosis of pancreatic tumor. Postoperative histopathology was reported as gastrointestinal stromal tumor. Stainning with CD117, CD34, and actin was detected while there was no staining with S100, desmin, CD99, and CD138. Proliferative index was around 1–2% with Ki-67. Hypoglycemia and hyponatremia was developed postoperatively. Insulin and C-peptide levels were normal during hypoglycemia. All of the anterior pituitary hormones were low. L-thyroxine therapy was started after steroid replacement. Dextrose and isotonic NaCl replacement was performed. In the follow-up hypoglycemia and hyponatremia was improved. Sella was larger than normal in pituitary MR. Lobulated mass (pituitary adenoma?), was detected in sella, with size of 28×26×24 mm, showing heterogeneous staining with contrast material, compressing optic chiasm and bilateral optic nevre, and causing lateral cavernous sinus invasion. Nonfunctional pituitary adenoma pituitary was detected as a result of the operation.
Result
GISTs are a rare type of gastrointestinal tumours that are most commonly located in the small bowel or stomach but can also be found in the duodenum. Gastrointestinal stromal tumors may be associated with pituitary adenomas. This issue must not be ignored and has to be examined in this respect.

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P214

New-onset autoimmune disorders after successful treatment of Cushing's disease

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Background
Excessive level of cortisol in patients with Cushing's disease (CD) can cause an immunosuppression. Therefore after resolution of hypercorticism the underline autoimmune disorders can appears.
Aim
We are presenting three cases of autoimmune disorders diagnosed in patients successfully treated for CD.
Results
Case 1: Woman, 37-year-old with confirmed panhypopituitarism after transsphenoidal adenomectomy (TSA) for CD in June 2013. Panhypopituitarism was replaced by hormonal therapy. Several months later she complained for arthralgia and painful erythematous nodules in soft tissues of shins. Erythema nodosum was diagnosed. After increasing the dose of hydrocortisone the lesions disappeared.
Case 2: Woman, 33-year-old In active state of CD pneumonia was diagnosed. She was treated by antibacterial therapy with resolution of symptoms. In May 2013 TSA has been done. Panhypopituitarism was compensated by hormonal therapy.

Four months later she complained for caught, subfebrile temperature and appearance of painful erythematous nodules in soft tissues. After clinical evaluation pulmonary sarcoidosis and erythema nodosum were diagnosed. The dose of glucocorticoids was significantly increased and she felt herself better. Reduction of the dose has led to exacerbation of symptoms of sarcoidosis and erithema nodosum again.
Case 3: Woman, 43-year-old panhypopituitarism developed after TSA for CD in July 2011 and was compensated by hormonal therapy. Twelve months later the diffuse toxic goiter occurred. L-thyroxine was cancelled and methimazole was prescribed. Six months later thyroidectomy was done because of frequent relapse of thyrotoxicosis on low doses of methimazole accompanied with severe decompensation of secondary adrenal insufficiency.
Conclusion
There are limited reports of occurrence or relapse of underline autoimmune disorders after successful treatment for CD. The occurrence of sarcoidosis is very rare and not clearly understood. In case 2, more likely the sarcoidosis, but not pneumonia was in active state of disease.

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An unusual clinical presentation of Sheehan's syndrome: Co-occurrence of bycitopenia, acute colonic pseudo-obstruction and acute renal failure

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Sheehan's syndrome (SS) may be defined as development of anterior pituitary ischemic necrosis, first of which is caused by failure to meet the blood build-up required due to pituitary expansion secondary to lactotroph cell proliferation during pregnancy. Vasospasm, thrombosis and vascular compression of hypophyseal arteries have been described among the possible causes of SS. Additionally, expansion of pituitary gland, small sella, disseminated intravascular coagulation (DIC) and autoimmunity may as well play a role in pathogenesis of SS. SS is characterized by the loss, to varying degrees of anterior pituitary functions. We aimed to present a case with bicytopenia who was treated being diagnosed in our clinic with colonic pseudo-obstruction, acute renal failure, and SS as well, and discharged with full remission after treatment.
Case presentation
A 67-year-old female patient was admitted to our emergency department with the complaint of constipation, reduction of amount of her urine, and deterioration of general health. In medical history, she had been unable to pass gas and defecate for the last three days. She had ten children. She had given birth her last child when she was 38 years old. Her last child lived for ten days and never been breastfed. After she born her last child her menstrual cycle ceased. In the systemic examination, we detected cachectic appearance, extensively decreased skin turgor (tone), absent axillary hair, pale skin and conjunctivae in her physical examination. A 7 cm subcostal incision scar secondary to abdominal cholecystectomy was found and hypoactive bowel sounds were heard (1/min). The first laboratory tests in the Emergency Clinic were below: Glucose: 72 mg/dl, Urea: 65 mg/dl, Crea: 2.4 mg/dl, Na: 126 mmol/l, K:6.7 mmol/l, Calcium: 7.9 mg/dl, Alb: 4 gr/dl, AST: 78 U/l, ALT: 13 U/l, LDH: 669 U/l (220–480), amylase:160 U/L (28–100), Mg: 1.63 mg/dl (1.58–2.55), Total protein: 7.5 gr/dl, CK: 2795 U/l (2–190). WBC: 6400/mm^3, RBC: 2,72 /mm^3 (4-5.5), Hgb: 8.6 g/dl, PLT: 114.000/mm^3 (150–450), MCV: 94 fl, RDW: 16.4% (11.5–14), D dimer: 0.5 mg/l (0–0.55) and fibrinogen: 302 mg/dl (180–350). Erythrocyte morphology was normochromic normocytic. The plain abdominal radiograph in standing position reviewed in Emergency Clinic showed air-fluid levels. Colonic pseudo-obstruction was found in abdominal computerized tomography.
We consider hypopituitarism due to absent axillary hair, hypotension, hyperpotassemia and hyponatremia. Basal hormone results (8 a.m.) as below: Cortisol: 4.75 μg/dl, ACTH: 23.5 pg/ml (0–46), FT3: 0.28 pg/ml (2.1–5.2), FT4: 0.21 pg/ml (0.8–1.76), TSH: 4.8 mIU/l and Growth Hormone $<$0.05 ng/ml (0–8), FSH: 4.97 mlU/ml (9.7–111), LH: 1.26 mlU/ml, Estradiol: 29.2 pg/ml (20–30), Progesterone $<$0.2 ng/ml (0–1), DHEAS $<$15 μg/dl (35–430), IGF-1 (Insulin-like growth factor) $<$25 ng/dl (71–290), prolactin: 0.72 ng/ml (1.8–20.3) and Total Testosterone: 0.01 ng/dl (0–74). Synacthen stimulation test and glucagon stimulation test were performed. But, low serum cortisol levels were found in both stimulation tests. Afterwards, in pituitary magnetic resonance examination, partially empty sella was detected in the patient**.** She discharged with full remission after hormone replacement treatment.
In conclusion, SS is not a very rare condition in our developing country. However, SS is insidious condition. Because obscure of complaints and clinical findings are similar to that of many other diseases, the diagnosis of SS is delayed. Moreover, SS with unusual clinic presentation cannot be considered in differential diagnosis. In order to diagnose SS patients before occurrence of complications, as in our case, a proper anamnesis should be performed and clinical findings should be interpreted carefully.

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Challenges in the diagnosis of pheochromocytoma: a case report

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Introduction
Adrenal pheochromocytomas are rare neuroendocrine tumours and their prevalence is likely underestimated – in some series 50% of cases were diagnosed during autopsy. The clinical presentation varies among patients which may make the diagnosis difficult to establish. We present the case of a woman with certain clinical characteristics of pheochromocytomas and who was diagnosed after having suffered a stroke. Specific points suggesting a pheochromocytoma and critical to the clinical practice are discussed.
Case report
A 49-year-old woman with hypertension and a suspected pheochromocytoma was referred to the Endocrinology Department in Wrocław. The patient underwent two surgeries for paragangliomas of the right and left carotid artery. During the second surgery, the patient suffered a stroke. After administrating anticoagulants, a bleeding from the gastrointestinal tract occurred. During the diagnostic process CT of the abdomen revealed a tumor in the right adrenal gland. Significantly elevated catecholamines and their metabolites in blood and urine confirmed the pheochromocytoma diagnosis; the patient was also diagnosed with diabetes. On account of the patient's past paraganglioma incidents and her family history (sister), we also began genetic screenings for hereditary pheochromocytoma. A mutation in the *SDHD* gene was revealed in the patient's DNA and subsequently in the blood samples taken from her sister and daughter.
Conclusions
Occurrence of paragangliomas with hypertension suggests the need for the pheochromocytoma–paraganglioma syndrome screening, especially in the case of paragangliomas in a patient's family history. Early treatment is crucial to avoid life-threatening cardiovascular complications.

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A huge metastatic adrenocortical carcinoma presenting with Cushing's syndrome and inferior vena cava thrombosis: case report

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Background
Adrenocortical carcinoma (ACC) is a very rare but typically aggressive malignancy. About one to three quarters of ACC is functioning with excess hormonal production.
Case
A 44-year-old female patient was admitted to out-patient clinic with obesity, oligomenorrhea and abdominal pain. She had central obesity, buffalo hump, and palpable flank mass. Hypertension, transient ischemic attack, and epilepsy history was present.
Serum cortisol, DHEAS, and testosterone levels were elevated. Cushing's syndrome was diagnosed by elevated urine free cortisol and a non-suppressible

dexamethasone test. Serum aldosterone and renin activity, 24 h urinary catecholamines were normal.
Abdominal CT detected a 16×11 cm hypodense solid mass lesion at the right adrenal gland. It showed inhomogeneous appearance, irregular margin, neovascularization, liver invasion, and inferior vena cava (IVC) thrombus extension (2.3–2.2 cm). It was adherent to the liver, kidney, and IVC.
Because of the unresectable adrenal mass, CT-guided abdominal mass biopsy was performed, and the diagnosis of ACC was made on the basis of pathology and immunohistochemistry. According to the AJCC staging system, the tumor was classified as T4NXM1, stage IV.
Mitotane 4.5 g/day and glucocorticoid was started. Also, coumadin was started due to presence of thrombus. The mean level of total testosterone and DHEAS tended to decrease during the follow-up.
After 5 month, radiotherapy and chemotherapy (cisplatin and etoposide per three cycle) were given to patient. Tumor regressed to 10–7.6 cm with IVC thrombus extension (2.2–1.4 cm). The patient showing partial remission underwent operation, but because of invasion to adjacent tissues, the tumor could not be resected.
Conclusion
Adrenal tumors in association with venous thrombosis are a rare pathological condition. No effective adjuvant treatment is currently available. We report a case of stage IV adrenocortical cancer with IVC thrombus extension and partial clinic response to the chemoradiotheraphy.

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Synchronous acromegaly and gastrointestinal stromal tumor: a case report

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Introduction
Synchronous and asynchronous cases of acromegaly and other malignancies have been reported in literature. However, synchronous apperance of acromegaly and gastrointestinal stromal tumors (GIST) is encountered so rarely. We herein reported a case of synchronous acromegaly and GIST.
Case report
A 59-year-old patient was investigated due to iron deficiency anemia. On the physical examination revealed enlarged hands and coarse facial feature; and, several discrete skin tags were detected. The laboratory findings were as follows: hemoglobin, 8.6 g/dl; hemotocrit, 28.8%; GH, 5.14 ng/ml; and IGF1, 820 ng/ml (normal range: 81–225 ng/ml). Oral glucose tolerance test of 75 g was performed, and GH values were unsuppressed (GH, 3.60 ng/ml at min 0; GH, 4.20 ng/ml at min 30; GH, 4.29 ng/ml at min 60; GH, 4.50 ng/ml at min 90; and GH, 1.80 ng/ml at min 120). Pituitary magnetic resonance imaging revealed a left pituitary microadenoma of 7 mm, and so the case was diagnosed with acromegaly. Endoscopy of upper gastrointestinal tract revealed an ulcerovegetan mass in duedonum. Biopsy was performed, and as a result of the histopathological investigation, a tumoral lesion with spindled-pattern cells with centrally placed nucleus, pale eosinophilic cytoplasms and forming ill-defined fascicles was observed. Immunohistochemical stains indicated the following results as positive ones: CD117 (c-kit), CD34 and vimentin, and negative ones: S100 and desmin. The case was diagnosed with GIST. The patient diagnosed with acromegaly and GIST was operated on due to GIST. After GIST operation, the case was started to be administered with somatostatin analogue to treat acromegaly because of the patient's refusal of pituitary surgery.
Conclusion
The involvement of IGF system in GIST was indicated in literature. However, the association between acromegaly and GITS is not known exactly.

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Cognitive impairment in a patient with a TART syndrome

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Introduction
In the testicular adrenal rest tumor (TART) syndrome, doctors think before all to preserve fertility and oncological risk. Meanwhile, for the patient are relevant primarily those disorders that hinder him daily functioning and affect the quality of life. Because of it, we would like to introduce our patient with cognitive impairment.
Case report
A 20-year-old male, working in the factory, came to an endocrinologist at the request of his mother's. In the family is known a history of 21-hydroxylase deficiency in the classic form with the loss of salt. The patients have a substitution of hydrocortisone from the neonatal period. In medical examination we find tumorous changed testes. Our attention drew a very high ACTH (1933 pg/ml) and 17-OH-progesterone (>19 ng/ml) with normal testosterone (4.3 ng/ml). The examination of cognitive function (TYM test 20/50) indicated a mild degree of dementia.
The patient admitted that he often forgets about taking drugs and generally has a growing feeling of bad memory. In pediatric medical history we find information testicular tumorous changes disappearing when ACTH levels normalized during the regular substitution.
Cognitive and executive dysfunctions have been described in 21-hydroxylase deficiency, more common in women. It is difficult to decide whether an important pathogenic factor is, an excess of glucocorticoids, their insufficient substitution and/or associated increase of ACTH or whether cognitive impairment a independent of disorders resulting from 21-hydroxylase deficiency. But we cannot rule out the mechanism vicious circle, where irregular intake of drugs affects memory and memory disorders impede regular medication.
Conclusion
According to our knowledge this is the first report of cognitive impairment in TART syndrome.

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Neuropsychiatric aspects in a rare case of hypothalamic obesity

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A 22-year-old woman presented with weight gain (class I obesity), oligomenorrhea, impaired vision, and altered concentration. With suspected craniopharyngeoma she was treated with transcranial surgery; in fact for a suprasellar haemangioma. Post-operatively, she still presented an alteration in appetite with hyperphagia and excessive weight gain up to class III obesity. This syndrome is described as 'hypothalamic obesity' and results from any damage to the ventromedial hypothalamus potentially leading to autonomic imbalance, hyperphagia, insomnia, and pituitary deficiency. Endocrine diagnostics revealed panhypopituitarism in our patient. Furthermore, she suffered from anhidrosis and an altered thermoregulation with an increase of body temperature up to 40 °C during low physical activity, which makes it nearly impossible to loose weight through training programs. Obesity and hyperinsulinemia led to development of diabetes mellitus. Lifestyle intervention is described essentially useless in this syndrome. Appropriate hormone replacement therapy and strict caloric reduction showed slight effect on weight loss in her case. Bariatric surgery is still planned for the future, although there are no data on metabolic outcome and long-term results in patients with hypothalamic syndrome. Further diagnostic procedures showed a central sleep apnea syndrome with hypoxemia, alteration in cognition, learning, and memory processes as well as an organic affective disorder with loss of motivation and increased daytime sleepiness. Only a few numbers of studies have investigated neuropsychological deficits and development of functional capacities in patients with hypothalamic obesity syndrome, mainly due to craniopharyngeoma during childhood, so far. Limited numbers of therapeutic trials yield no standard pharmacological intervention. There is evidence that deficits in hypothalamic–pituitary axis itself lead to alteration of neuropsychiatric functions and obesity is known to be associated with affective disorders like depression, additionally. Therefore, patients with hypothalamic syndrome seem to be at great risk of developing psychiatric diseases with impaired quality of life. Besides effective substitution therapy for hypopituitarism and strict life-style interventions to control weight, one should be aware of possible neuropsychiatric disorders and included psychotherapy if necessary.

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P221

A case with APECED syndrome

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Introduction
APECED syndrome is characterized by the three most common components of the condition, i.e. mucocutaneous candidiasis, autoimmune hypoparathyroidism, and Addison's disease. Presence of two of these components suffices for diagnosis.
The case
A 33-year-old female patient presented to the endocrinology polyclinic for weakness, nausea, vomiting, dizziness, recurring vaginal itch, and discharge for 1 year, intermittent dysphagias and amenorrhea in July 2013. With no relevant findings in her history or familial history, the patient's physical examination revealed orthostatic hypotension, oral angular stomatitis, geographic tongue and ulcerative lesion on the tongue and bilateral nail dystrophy and her vaginal examination demonstrated white plaques consistent with candidiasis. Biochemical investigations yielded the following results: basal cortisol: 3 μg/dl (6.2–19.4), short Synacthen test: 0 min, cortisol: 3 μg/dl 30 min: 3 μg/dl. aldosterone: 7 pg/ml (29.4–161.5), plasma renin: 46 ng/l (3–16), FSH: 44.2 mIU/ml (postmenopausal 25.8–134.8), LH:58 mIU/ml (postmenopausal 7.7–59), estradiol $<$ 20 pg/ml (postmenopausal 5–54). Other laboratory test results were normal. Gastroscopy as performed and the results were consistent with candidal esophagitis, decreased esophageal peristaltism and antral gastritis. The patient with primary adrenal insufficiency, chronic mucocutaneous candidiasis, ectodermal dystrophy, primary hypogonadism was diagnosed with APECED syndrome. The patient was also started on treatment with prednisolone 7.5 mg/day, fludrocortisone 0.1 mg/day, norgestrel + estradiol valerate tablets 1×1 and placed under follow-up of endocrinology polyclinic and gastroenterohepatology polyclinic.
Conclusion
Patients who present with primary adrenal insufficiency may have isolated adrenal insufficiency but this may also be a component of autoimmune endocrinopathy or APECED syndrome, as was in our patients. If left untreated, systemic candidiasis may lead to untoward consequences which may be as severe as esophageal perforation, especially in the presence of esophageal involvement. Therefore, patients with primary adrenal insufficiency must be investigated carefully for other concomitant hormone deficiencies and systemic candidiasis at the time of their initial presentation.

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Hyponatremia as a first symptom of hypopituitarism in an adult patient with natural history of craniopharyngioma undiagnosed since childhood

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Background
Craniopharyngiomas may lead to pituitary insufficiency and neurological symptoms. However the rate of the tumor growth and the time of developing hypopituitarism are difficult to predict.
Case report
A 68-year-old male of short stature (height 148 cm) was admitted to the area hospital due to loss of consciousness. The acute coronary syndrome and stroke had been excluded but laboratory tests showed hyponatremia of 106 mmol/l. Hormone measurements were as follows: ACTH, 6 pg/ml; cortisol, 1.6 μg/dl; TSH, 0.818 μIU/ml; fT_4, 7.7 pmol/l; $fT3$, $<$1.0 pg/ml; LH, $<$0.1 IU; FSH, 0.282 IU/l, DHEA-S, $<$150 ng/ml; testosterone, $<$0.2 ng/ml; PRL, 0.78 μg/l; GH, $<$0.1 μg/l; and IGF1: $<$25 μg/l. The physical examination revealed the absence of testes in the scrotum and lack of pubic hair. MRI demonstrated a pituitary tumor consistent with craniopharyngioma measuring $31\times34\times35$ mm, enveloping cavernous sinuses and internal carotid arteries. Densitometry showed L1–L4 *T*-score: −4.8. A CT scan revealed the presence of undescended testes measuring 15 mm in the inguinal canals. Owing to pituitary insufficiency a replacement therapy with hydrocortisone and L-thyroxin was initiated, leading to improvement in general condition as well as normalization of sodium level. Additionally, the intravenous bisphosphonate and vitamin D was started. The patient remains in stable state and refuses the possibility of surgical treatment.
Conclusions
The case described demonstrates a natural history of craniopharyngioma, developing since birth or even fetal life, with gradual deterioration of pituitary function – first manifested by gonado- and somatotropic dysfunction, and several decades later followed by thyreo- and corticotropic deficiency. Moreover, in management of hyponatremia a possibility of secondary adrenal insufficiency and hypothyroidism due to a pituitary tumor should be considered. In such cases, initiation of hydrocortisone and thyroxin treatment can be life-saving.

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Ineffectiveness of temozolomide in aggressive dopamine-agonist resistant prolactinoma and type 3 silent somatotropinoma

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Introduction
Temozolomide (TMZ) can be administered as the last therapeutic option for aggressive pituitary tumors. Dopamine-agonist resistant prolactinomas are relatively frequent and remain a serious therapeutic problem. GH expressing atypical adenomas are rare and their positive response to TMZ is low. In a general opinion a lack of response to TMZ after three cycles predicts the treatment resistance.
The aim of the study was presentation of two patients with a long-standing history of atypical aggressive pituitary macroadenomas, refractory to numerous medical and ablative therapies and also to TMZ treatment.
Case 1
A 59-year-old woman with MEN1 syndrome (prolactinoma and primary hyperparathyroidism). Because of amenorrhea–galactorrhea syndrome she received dopamine agonists for 16 years. The tumor size was stable for 10 years, but PRL level was never normal. Five years ago, propter tumor expansion and resistance to dopamine-agonists she underwent non-total transsphenoidal adenomectomy but further enlargement of prolactinoma and its multidirectional expansion succeeded. She was disqualified for the next neurosurgery and gamma-knife and TMZ was implemented. Unfortunately TMZ was ineffective and it was withdrawn after three cycles.
Case 2
A 44-year-old woman with hormonal inactive macroadenoma causing secondary hypogonadism and compression of the optic chiasm. She underwent a left temporal craniotomy with subtotal adenomectomy followed by cobaltotherapy. A postoperative exploration revealed adenoma chromophobum. 18 years later, due to a re-growth of the tumor, she underwent right craniotomy. The second postoperative study revealed atypical GH (+), PRL (+) – type 3 silent adenoma. Then $^{90}Y/^{177}Lu$ DOTA-TATE, somatostatin analogue and bromocriptine were applied. Symptoms of acromegaly occurred only after 19 years from the diagnosis. Propter large tumor size and its localization the patient was disqualified for neurosurgery and gamma–knife. Three cycles of TMZ were administered without any response.
Conclusion
Long-standing, large atypical invasive pituitary dopamine-agonist refractory prolactinomas and silent somatotropinomas may be refractory to temozolomide treatment.

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P224

Cushing's disease in patient with primary empty sella

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Introduction
The empty sella syndrome (ESS) is defined as the penetration of the subarachnoid space into intrasellar region. In ESS pituitary hormonal function is usually

normal, but several, mostly subtle, hormonal abnormalities have been also reported. The coexistence of Cushing's disease and primary empty sella is very rare.
Objective
The presentation of an exceptional case of a patient with Cushing's disease associated with primary empty sella.
Case report
A 70-year-old woman with typical clinical signs of hypercortisolism observed from 11 years. She presented visceral obesity, diabetes and severe hypertension (diagnosed as metabolic syndrome), plethora, thin skin, hemorrhagic diathesis, proximal limbs muscle atrophy, and weakness. Endocrine evaluation of adrenocortical axis proved hypercortisolism of pituitary origin with a loss of ACTH (28.48–28.2 pg/ml) and cortisol (30.0–18.8 μg/dl) circadian rhythms, increased urinary cortisol excretion (693 μg/dl per day), a lack of cortisol suppression after low dexamethasone dose and the presence of suppression after high dexamethasone dose. MRI disclosed subarachnoid cyst (18×16×15 mm) and an empty sella. The pituitary was compressed with the altitude of its anterior lobe of about 3 mm. Abdominal CT revealed bilateral homogenous adrenal hypertrophy without focal changes. Despite of a lack of visible microadenoma on MRI scans, on the base of clinical and laboratory findings, the patient was prepared to neurosurgery with a steroidogenesis inhibitor – ketoconazole. A pituitary microadenoma was removed by the transsphenoidal approach. A postoperative pathologic exploration revealed densely granulated corticotroph adenoma. After the neurosurgery, the patient experienced severe secondary hypoadrenalism and hydrocortisone replacement treatment was administered. Other pituitary trophic hormones remained normal.
Conclusion
It is worth emphasizing that metabolic syndrome together with an empty sella syndrome did not rule out a pituitary corticotroph adenoma.

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P225

Temozolomide-induced marked regression of invasive Crooke's cells corticotropinoma in patient with Cushing's disease

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Introduction
Crooke's cells are normal corticotrophs with cytoplasmic accumulation of cytokeratin filaments in response to glucocorticoids excess. Crooke's cell corticotropinomas are the unique cause of Cushing's disease. Nearly all of them are invasive macroadenomas, generally aggressive, refractory to conventional therapy, with high recurrence rate.
Aim of the study was to present a case study of a patient with Cushing's disease caused by Crooke's cell corticotropinoma which was resistant to multiple neurosurgery approaches but susceptible to treatment with temozolomide (TMZ).
Case report
A 51-year-old man with Cushing's disease diagnosed 4 years earlier. He presented a clinical picture of hypercortisolism with high ACTH concentrations, loss of cortisol circadian rhythm, increased urinary cortisol excretion and a lack of suppression after low and high dexamethasone dose. MRI revealed 32×29×24 mm macroadenoma. The patient underwent subtotal selective transsphenoidal adenomectomy without hypercortisolemia retirement. A postoperative pathologic exploration revealed a rich granulated corticotroph (only ACTH plus) Crooke's cells adenoma with MIB1 index $<1\%$. Owing to a re-growth of the tumor he underwent two consecutive non-total transsphenoidal reoperations. Because of the large size of the tumor with its expansion to both cavernous sinuses and suprasellar region together with a compression of the optic chiasm, the patient was disqualified for gamma-knife. Owing to a bad prognosis and exhaustion of all conventional therapeutic options the patient was admitted to our department for qualification to TMZ. The standard schedule and dose of TMZ (150–200 mg/m^2 for 5 days every 28 days) were implemented. As early as after three courses of TMZ, the pronounced regression of tumor size with marked hormonal and clinical improvement was certified. After six courses consecutive tumor regression was observed. Nine courses resulted in almost total radiological tumor regression and hormonal normalization.
Conclusion
Temozolomide can be an effective treatment option in invasive Crooke's cell cortcotropinoma.

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P226

Treatment of aggressive corticotropinoma with temozolomide and bevacizumab in patient with Nelson's syndrome

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Introduction
Aggressive corticotropinomas are more invasive than other pituitary tumors. Recent reports have documented the efficacy of temozolomide alone or in combination with an anti-angiogenic agent –bevacizumab in invasive pituitary adenomas treatment.
Objective
Presentation a case of 56-year-old woman initially diagnosed as Cushing's disease and the analysis of treatment procedures with special concentration on temozolomide and bevacizumab.
Case study
At the moment of diagnosis she presented a clinical picture of severe hypercortisolism with high ACTH concentration, loss of cortisol circadian rhythm, fivefold increased urinary cortisol excretion and a lack of cortisol suppression after low and high dexamethasone dose. The ectopic source of ACTH was excluded. MRI revealed 9×7 mm microadenoma. The patient underwent selective transsphenoidal adenomectomy followed by a 27-month-long period of remission. A postoperative exploration revealed a sparsely granulated corticotroph adenoma with MIB-1 index of about 40%. Due to a re-growth of the tumor she underwent two transsphenoidal reoperations followed by stereotactic radiotherapy. Afterwards, because of treatment failures, bilateral total adrenalectomy was performed. Then the patient developed Nelson's syndrome. A fourth transsphenoidal adenomectomy was performed, but there was a rapid recurrence of the tumor with an expansion to the right cavernous sinus and suprasellar region with a compression of the optic chiasm causing blindness of the right eye. Five months later she underwent a right fronto-temporal craniotomy with subtotal suprasellar adenomectomy. Propter a rapid re-growth of the tumor the patient was disqualified for gamma-knife and received cabergoline and somatostatin analogue for some time. Only nine cycles of TMZ resulted in marked clinical, biochemical and radiological improvement. After 6 months pause in temozolomide a consecutive relapse occurred. Then bevacizumab was introduced. Until now the clinical stabilization of the disease has been observed.
Conclusion
Temozolomide alone or in combination with bevacizumab can be an effective treatment option in invasive corticotropinomas.

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P227

Meningitis coexisting with pituitary macroadenoma: report of two cases

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Background
Meningitis coexisting with pituitary macroadenoma is rarely observed. It occurs either as a primary meningitis (primary tumor manifestation), or as a secondary meningitis (after neurosurgery or reduction of the volume of the tumor which has destroyed the sellar floor or the skull base).
Objective
Case reports of two patients with the concomitance of secondary meningitis and pituitary macroadenoma.
Case 1
A 36-year-old man treated with dopamine agonist because of hyperprolactinemia due to pituitary macroadenoma. In MRI a solid tumor mass with cystic components (2.6×3.7×3.6 cm) was described. Hyperprolactinemia and partial hypopituitarism (adrenal, thyroid and gonadal insufficiency) were present. After 1 year of treatment, partial tumor regression, PRL normalization and improvement of pituitary function were observed. During the 3rd year of the illness purulent meningitis was diagnosed with a subsequent complete loss of pituitary function. MRI showed a cystic sellar mass (3.0×2.9×3.2 cm) with ring, intense, irregular, peripheral enhancement after a contrast injection. A transsphenoidal excision was done. Post-surgical study revealed the pituitary abscess.
Case 2
A 42-year-old woman with acromegaly diagnosed 8 years earlier. In MRI a giant adenoma (5.5×3.7×3.2 cm) spreading to cavernous sinuses, sphenoid sinus and suprasellar region was certified. The patient received somatostatin analogue and

1 year later she underwent partial transsphenoidal adenomectomy. A post-operative pathologic examination revealed pituitary adenoma: GH(+++) and PRL(+++). After neurosurgery somatostatin analogue and bromocriptine were continued. Four years later the patient was admitted to hospital due to purulent meningitis. After the meningitis healing the tumor size and pituitary function remained unaffected.

Conclusions

Despite the fact that meningitis coexisting with pituitary macroadenoma is rare, we should remember that it can occur both before and after neurosurgery. It may result in a full recuperation or in aggravation of earlier endocrine disturbances with a specific complication such as a pituitary abscess.

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P228

Primary hyperaldosteronism presenting as hypokalemic periodic paralysis: two case reports

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Background

Hypokalemia is a chronic condition in primary aldosteronism (PA) and hypokalemia symptoms usually can be tolerated by the patients. Hypokalemic periodic paralysis due to primary aldosteronism is rarely reported. We reported two cases of hypokalemic paralysis due to primary aldosteronism.

Case 1

A 33-year-old male admitted to the emergency service with fatigue, numbness, progressive weakness in his legs and arms for 2 months. He had a hypertension for 8 years and his medications were triple antihypertensive. On physical examination his blood pressure was140/90 mm Hg, upper and lower extremity muscle strength loss. Laboratory results were revealed low potassium levels (1.4 mEq/l) and high creatine phosphokinase (CPK) levels (1465 IU/l). The patient was hospitalized with a prediagnosis of hypokalemic periodic paralysis. After normalizing potassium level plasma aldosterone concentration (PAC) and plasma renin activity (PRA) were 60 ng/dl (7–30 ng/dl) and 0.6 ng/ml per h (0.7–3.3 ng/ml per h), respectively and PAC:PRA ratio was 100 and saline infusion test was confirmed primary aldosteronism. MRI revealed a 12 mm adenoma in left surrenal. Left surrenalectomy was performed after 200 mg/day spironolactone treatment. Post-operative pathology result was adrenal cortical adenoma.

Case 2

A 39-year-old woman applied to hospital with recurrent muscle pain and muscle weakness. Physical examination of patient revealed 150/80 mmHg, upper and lower extremity muscle strength loss. Laboratory measurements showed low potassium level (1.7 mEq/l), elevated CPK level (1825 IU/l) and metabolic alkalosis. Hypokalemic periodic paralysis was suspected and after normalizing potassium level PAC and PRA were 46 ng/dl (7–30 ng/dl) and 0.3 ng/ml per h (0.7–3.3 ng/ml per h) respectively. PAC to PRA was 153.3. Primary aldosteronism was confirmed with saline infusion test. Other endocrinologic tests were normal. MRI revealed 15×9 mm adenoma in left surrenal. Spironolactone was added and left surrenalectomy was performed to the patient. Histopathologic diagnosis was adrenocortical adenoma.

Conclusion

Hypokalemia may cause proximal muscle weakness, cramps, fatigue, polyuria polydipsia, nocturia, rhabdomyolysis and hypokalemic periodic paralysis. PHA patients may be misdiagnosed with polymyositis due to high CPK levels and guillain barre syndrome due to quadriparalysis. Therefore, when patients are admitted with symptoms indicating hypokalemia, potassium levels should be measured and if hypokalemia and hypertension is observed PHA should be examined.

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P229

A case of hypopituitarism caused by lung cancer metastasis to the pituitary

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Pituitary tumor is a rare endocrine disorder. In the majority of cases, they are secreting prolactin and/or GH. Pituitary metastatic tumors are localized more often in the nervous than adenomatous hypophysis. Lung, breast and large intestine cancers metastases are found in the pituitary in the most cases. They cause hypopituitarism and local complications. The most often complications found are an optic nerve chiasm pressure or infiltration with a visual field loss, cavernous sinus infiltration, bone destruction, pressure and infiltration of the local brain regions, increased intracranial pressure. Headaches and ophthalmoplegy are often not connected to hypopituitarism, but an aggressive neoplasm.

We reported 67-year-old man referred from General Practitioner to hospital admission due to vertigo, syncope, visual loss and pituitary tumor revealed in the CT scans. The tumor infiltrated bones, soft tissues, the optic nerve chiasm also and caused progressive visual field loss. The patient had prostate cancer diagnosed and treated some years before. Secondary hypothyroidism, adrenal insufficiency and hypogonadotropic hypogonadism were shown. An X-ray chest scan revealed not significant right pulmonary recess enlargement. The right pulmonary recess diagnosing was postponed, due to fast progressive patient's bilateral visual loss. Suitable replacement therapy was prescribed. The man was referred to an urgent neurosurgery. Tumor histopathological examination revealed small-cell cancer. Then patient was referred to Pulmonary Clinic, where small-cell lung cancer with pituitary and liver metastases was diagnosed. There was no response to palliative chemotherapy, patient died due to lung cancer progression.

Pituitary metastatic tumors, although rare in general, often appeared in metastatic cancers. The presence of an invasive pituitary tumor should indicate a need to looking for a malignant lesion.

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P230

Transient severe polyuria in a patient with bilateral pheochromocytoma after adrenalectomy

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Background

Postoperative severe polyuria is a rare condition after adrenal pheochromocytoma resection. We presented this case due to its rarity.

Case

A 50-year-old women admitted to emergency service with malaise and fatigue complaint. The patient was using triple antihypertensive combination that started 10 years ago. Her medical history included cerebrovascular event due to hypertension 5 years ago. In physical examination her BMI was 20 kg/m^2, her pulse was 110 beats/min, her blood pressure was 160/100 mm Hg, Left upper and lower extremity were plegic. Laboratory evaluation revealed low potassium level (2 mEq/l). Patient was hospitalized to investigate the causes of hypertension and hypokalemia. After potassium normalization PAC:PRA ratio were normal. Urine metanephrine and normetanephrine levels were 7269.7 μg/day (52–341 μg/day) and 689.76 μg/day (88–444 μg/day) respectively. MRI revealed 34×33×32 mm mass in right adrenal gland and 57×52×45 mm mass in left adrenal gland, both mass had hyperintens in T2weighted images. Preoperatively doxazosin, amlodipin and metoprolol were started. Intravenous fluid was replaced as well. Left adrenolectomy was performed to patient for pheochromocytoma and pathologic result was pheochromocytoma. Metanephrin and normetanephrin levels 1 week after left adrenolectomy were 129 and 11 742 μg/day respectively. After these results, under the umbrella of steroid right adrenalectomy was

performed as well. Pathologic result of right adrenalectomy was also pheochromocytoma. In postoperative first day urine output was 12 l/day and urine density, blood urea nitrogen were 1002 and 25 mg/dl (6–20 mg/dl) respectively but blood osmolarity and other electrolyte values were normal. ADH levels and other biochemical values were normal as well. Oral and parenteral fluid was replaced due to central venous pressure. Polyuria was continued for 5 days and after 6th day urine output decreased and urine density was improved.

Discussion

After adrenalectomy postoperative change of atrial natriuretic peptide, brain natriuretic peptide, adrenomedullin, ADH and urinary β2 microglobuline levels were thought to be responsible from polyuria. In our case the patient was suffered from a transient severe polyuria after bilateral adrenalectomy due to pheochromocytoma. We suggest that pheochromocytoma patients should be evaluated in terms of polyuria postoperatively.

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Macroprolactinoma that disappears in a short time with cabergoline treatment: case report

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Introduction

Prolactinomas are frequent in women and between 20 and 40 years but rarely seen in men especially as macroadenoma. Both in microadenomas and macroadenomes unless there is not any indication for an emergent surgery, first line treatment is always medical with dopamine agonists. In this report, we presented a patient with macroprolactinoma that disappears in a short time with dopamine agonist treatment.

Case

A 20-year-old boy admitted to endocrinology policlinic with complaints of headache for 9 months, short statue and delayed secondary sex characters. In initial physical examination his height, weight and BMI were 161 cm, 61.9 kg and 23.9 kg/m^{2}respectively. His axillary and pubic hair were tanner stage1, left and right testicle volume were 8 ml and enlarged penis length was 6.5 cm. Laboratory values revealed hyperprolactinemia (>200 ng/ml), hypogonadotropic hypogonadism and secondary hypothyroidism. Pituitary MR detected a 40×26×23 mm mass located in hypophysis that invades optic chiasma, sphenoid sinus and cavernous sinus. Eye examination showed a nasal visual field defect. Cabergoline 0.5 mg/per week and levothyroxine 100 μg/day were started and 2 weeks later cabergoline dose was increased to 2 mg/week. At 3th month patient's testosterone levels and prolactin levels were improved, hipophysis MR revealed that pituitary mass decreased to 21×15×22 mm. At 9th month of cabergoline treatment patient's right and left testicle volume were both 18 ml, enlarged penis length was 12 cm, axillary and pubic hair were tanner stage 2, laboratory values were all normal, pituitary mass was totally disappeared in MR and no visual defect was detected.

Conclusion

Macroprolactinomas are seen especially in males. In macroprolactinomas first line treatment is medical with dopamine agonists. Clinical presentation of prolactinomas in males are frequently hypogonadism and erectile dysfunction and these symptoms improves with treatment. In our case medical treatment with dopamine agonists was preferred and in a short time prolactinoma was totally disappeared, prolactine levels and hypogonadism were improved. We suggest medical treatment as first line treatment for macroprolactinoma unless there is a urgent surgery indication.

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A case of primary aldosteronism with the subclinical Cushing's syndrome examined the localization by double immunostaining for CYP11B1 and B2

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A 63-year-old woman was referred to our hospital for examination of three adrenal nodules. She had been diagnosed with hypertension since the age of 40 and prescribed antihypertensive drugs. Then, she was pointed out hypokalemia and bilateral adrenal tumors. She was diagnosed with primary aldosteronism (PA) at another hospital and had been prescribed spironolactone because the localization was not determined despite adrenal vein sampling (AVS) was performed.

Her parents had been suffering from hypertension and her daughter had been excised adrenal gland in Cushing's syndrome. She didn't have the cushingoid appearances, but her blood pressure was still high and hypokalemia had been continued. Abdominal MRI revealed three adrenal nodules (right 1 and 3 cm, left 1 cm). Three kinds of loading tests for the diagnosis of PA were all positive. Diurnal variation of plasma ACTH and cortisol was lost. 1 mg dexamethasone didn't suppress her cortisol. From these results, she was diagnosed with the coexistence of PA and subclinical Cushing's syndrome (SCS), AVS was performed to confirm the localization of each. Plasma aldosterone concentration was elevated at the right adrenal vein (11 800/149 000) (pre/post ACTH) (pg/ml). Cortisol of the right adrenal vein was not enough, but it would be suppressed by SCS at left adrenal gland (Left 86.5/805, Right 7.7/72.5) (pre/post ACTH) (μg/dl). However, larger nodule in the right adrenal gland also had the possibility of SCS, because SCS often caused by macro nodule. Hence, we examined the localization of SCS and PA by double immunostaining for CYP11B1 and B2 after the operation of the PA of the right adrenal gland. Surprisingly, CYB11B2 was stained at the portion of the larger nodule of right and CYP11B1 was stained the rest of it and small nodules of the right. This is the rare case of examined the localization by double immunostaining.

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P233

Primary thyroid lymphoma in a patient with adrenal incidentaloma

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Introduction

Primary thyroid lymphoma (PTL) presents between 2 and 8% of all thyroid malignancies. Rapidly enlarging neck mass, especially in women with Hashimoto's thyroiditis should steer the diagnostic procedures in the way of PTL. The most common type is diffuse large B-cell lymphoma. Adrenal incidentaloma are incidentally discovered adrenal masses without prior suspicion of adrenal disease.

Case report

A 71-year-old woman with an adrenal incidentaloma was admitted to our Clinic for regular annual testing. Her incidentaloma was first diagnosed 3 years ago. Ultrasound and CT confirmed left adrenal tumor of 15 mm in size. Annual endocrine evaluations showed normal midnight cortisol and basal ACTH with adequate cortisol suppression after 1 mg-overnight dexamethason suppresion test. Plasma renin activity (PRA) and aldosterone (ALD) were also in normal range with normal ALD:PRA ratio. Normal urinary catecholamines and serum chromogranine excluded active pheochromocythoma. Annual CT visualizations showed no change in tumor size during these 3 years. For the last 7 years she was taking levothyroxine due to hypothyroidism – Hashimoto's thyroiditis. Her thyroid status showed good substitution with elevated antithyroglobulin and antithyroid peroxidase antibodies. Ultrasound revealed recently enlarged thyroid mass with normal calcitonine. Surgery was performed after fine needle cytology. Pathohistology and immunohistochemistry showed B-cell lymphoma positive for CD3, CD5, CD43, PAX5, CD20 and partially positive for bcl2, CD43, with Ki67

of 25%. After surgery she received six cycles of chemotherapy. Overall she is doing well with good prognostic features.
Conclusion
The adrenal tumor was diagnosed three years before PTL and it did not show any change in size so it is most unlikely that this incidentaloma was of B cell lymphoma origin. According to the available literature this is the first case of PTL in a patient with most likely benign, nonfunctional adrenal incidentaloma.
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P234

Takotsubo cardiomyopathy triggered by pheocromocytoma crisis
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Introduction
Pheochromocytomas are a rare catecholamine secreting tumours that can mimic numerous stress-associated disorders, such as Takotsubo cardiomyopathy, or transient left ventricular apical ballooning which is brought on by an acute coronary vasospasm due to an excessive sympathetic stimulation.
Case Report
A 68-year-old woman, with previous medical history of hypertension and type 2 diabetes, who was on 30 units of isuline glargine, 850 mg metformin, 10 mg amlodipine, and 100 mg losartan per day, complained of epigastric pain and nausea and was initially suspected of having myocardial ischemia. ST segment elevation were noted on EKG in leads V2 and V3, and elevated ultrasensitive troponin levels were found in the blood test. She underwent coronary angiography, which did not show significant artery obstruction but revealed severe systolic dysfunction and akinesis of the mid-anterior, anteroapical and inferoapical segments. Her condition worsened in the following 24 h, and a total body CT scan showed a 7 cm tumor in the left adrenal gland. Urinary, and plasmatic catecholamines and metanephrines were consistent with pheochromocytoma. Treatment with phenoxybenzamine was initiated, improving patient's condition dramatically.
She underwent left adrenalectomy which confirmed that the tumor was indeed a pheochromocytoma. Three months after the surgery she is off medication for her diabetes and the cardiomyopathy has since resolved.
Conclusions
It is very important to consider Takotsubo in a patient presenting an acute coronary syndrome, and it is essential to rule out pheocromocytoma if such cardiomyopathy is suspected, because the early detection is crucial to the prognosis. The surgical resection of the adrenal mass might in most of the cases resolve the cardiomyopathy, and also prevent a fatal outcome due to a catecholamine crisis.
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P235

A history of 30 years severe uncontrolled hypertension: Conn's syndrome
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A 65-year-old Moroccan man was regularly followed in the outpatient clinic for type 2 diabetes since 2010 and was well controlled with an oral treatment. His past medical history included severe hypertension since 1985. Despite four antihypertensive agents, his blood pressure was not controlled (BP: 220/120 mmHg). A suspicion of renal artery stenosis was excluded by an invasive procedure.
He presented an impaired renal function (GFR: 50 ml/min) and his serum potassium level was 2.7 mmol/l. The renin aldosterone ratio at 26 and a high 24 h urinary aldosterone value, were compatible with a diagnosis of primary hyperaldosteronism. A 5 h rhythm of serum aldosterone/renin/ACTH/cortisol showed a correlation between aldosterone and ACTH/cortisol, but not with renin suggesting the presence of an adenoma.
CT scan of the abdomen showed a right adrenal mass ~1.2 cm in diameter. The results of the adrenal veins sampling correlated with a right lateralization.
He was referred for adrenalectomy, which was carried out laparoscopically. His blood pressure dropped and his serum potassium normalized, but he still needed treatment, although with less antihypertensive agents.
In the absence of proper treatment, patients with hyperaldosteronism suffer from poorly controlled hypertension, which may be associated with increased rates of stroke, heart disease, and kidney failure. Delay in the diagnose of hyperaldosteronism may be fatal.
Luckily it was not the case despite 30 years of undiagnosed Conn's syndrome.
Keywords
Hypertension, hyperaldosteronism, adrenalectomy
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P236

Unusual cause of hypoglycemia in a type 2 diabetic patient: panhypopituitarism
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We report on a 50-year-old patient of Moroccan origin, with insulin treated type 2 diabetes known for several years. He presented with a 6 months history of hypoglycemia, hypotension, associated with loss of libido and erectile dysfunction, anorexia, general deterioration and weakness. He had lost 20 kg over a 6-month period. The insulin doses were diminished from 70 to 42 U/day and the antihypertensive treatment was stopped due to repeated episodes of hypotension.
Laboratory results showed reduced free thyroxin with normal TSH and diminished morning serum cortisol levels. Besides, testosterone, LH and IGF1 levels were also reduced. The pituitary stimulation tests (TRH, LHRH, insulin induced hypoglycemia) revealed a delayed response in TSH, a delayed and prolonged response in LH, and no response in ACTH and GH. A MRI of the sella turcica revealed a macro adenoma with a left deviation of the pituitary stalk and a minimal compression of optical chiasma.
Findings were consistent with panhypopituitarism due to a pituitary adenoma. A replacement therapy was started including hydrocortisone, L-thyroxine and testosterone. Accordingly, symptomatology improved. The patient was then treated by endoscopic endonasal transsphenoidal adenomectomy leaving small amounts of healthy pituitary tissue. Immunohistology showed α-subunit positive cells.
Hypoglycemia and erectile dysfunction in a diabetic patient should not overlook other causes than excessive treatment and diabetes.
Keywords
Hypoglycemia, diabetes, erectile dysfunction, panhypopituitarism
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P237

Hyperprolactinemia secondary to primary hypothyroidism with hyperplasia pituitary
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Introduction
Although the most common causes of hyperprolactinemia are prolactinoma and iatrogenic, another possible cause is severe primary hypothyroidism, in which the increase of prolactin is a cause of pituitary stimulation by TRH, and can be presented with pituitary hyperplasia.
Case report
A 31-year-old woman who comes to endocrinology clinic for hyperprolactinemia, which was detected by symptoms of amenorrhea–galactorrhea. After normal pregnancy 4 years ago, she persisted with galactorrhea and menstrual irregularities; with persistence of secondary amenorrhea and

hypercholesterolemia in the last year. Sporadic headaches, no visual disturbances. Mild cold intolerance and some drowsiness. bilateral galactorrhea to expression. Normal palpable thyroid. Mild dry and pale skin. Minor bradypsychia. MRI: intrasellar tumor 1.5×1.2×2.5 cm which expands to sella. Homogenous contrast uptake. Involvement of the pituitary stalk and optic chiasm without invasion of the same. Invasion right cavernous sinus. Free T_4: <0.1 ng/dl, TSH: 684 μU/ml, PRL: 79 ng/ml. After checking the normality of the visual field, levothyroxine therapy was started at a dose of 100 μg/day. At 2 months of treatment, menstruation was restored although minimal galactorrhea persisted to the expression. At 6 months was repeated MRI, which was normal. At 20 m. became pregnant, requiring increase dose to 125 and then 150 μg/day. In the last months of pregnancy developed gestational diabetes and was controlled with diet only. She had a normal birth at term, not macrosomic and 6 months breastfeeding, menstruation recovery after the same; levothyroxine dose was reduced to 125, maintaining normal hormones.

Conclusions

In the study of hyperprolactinemia is required the determination of thyroid hormones, although imaging test is observed pituitary enlargement which can be considered as prolactinoma, because levothyroxine replacement therapy in cases of severe hypothyroidism to regularize both, hormone levels and pituitary hyperplasia, avoiding unnecessary treatments (dopamine agonist) or even neurosurgery.

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A rare cause of primary hyperaldosteronism unilateral adrenal hyperplasia: case report

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Introduction

Most common two causes of primary hyperaldosateronism are bilateral idiopathic hyperplasia and aldosteron secreting adenoma but unilateral adrenal hyperplasia is a rare cause. We presented a primary hyperaldosteronism case that caused by unilateral adrenal hyperplasia.

Case

A 56-year-old male admitted to endocrinology policlinic with complaints of polydipsia, polyuria, fatigue and muscle wasting. He had hypertension for 4 years. In physical examination blood pressure, pulse was 175/100 mmHg and 92 beat/min, respectively, Laboratory tests revealed hypernatremia (sodium 147 meq/l), hypokalemia (2.2 meq/l), increased creatinine kinase levels (1095 U/l), and metabolic alkalosis (pH 7.49, bicarbonate 35.9 mmol/l). After potassium correction plasma renin concentration (PRC), plasma aldosterone concentration(PAC), and PAC/PRC rate were 2.1 ng/l (5.3–99 ng/l), 401.5 pq/ml (38–313 pq/ml) and 200 pg/ml per ng per l (<50) respectively. In hormonal tests; TSH was 1.5 μIU/ml, cortisol was 14 μg/dl, urine catecholamine products were normal and dexamethasone suppression test was normal. Saline infusion test confirmed the diagnosis of primary hyperaldosteronism. Surrenal MR revealed a 18×16 mm adenoma in lateral limb of left adrenal gland. Spiranolactone treatment started and left surrenalectomy was performed. Pathologic evaluation detected adrenal hyperplasia that includes macronodular adrenal hyperplasia areas. The patient's potassium and blood pressure were normal postoperatively.

Discussion

Primary aldosteronism is characterized by hypertension and hypokalemia and caused by increased aldosterone production from adrenal cortex. Our patient had nephrogenic diabetes insipidus and muscle wasting due to hypokalemia. Hypokalemia is observed in 50% of aldosteron producing adenomas and 17% of hyperplasia. Unilateral hyperplasia mimics aldosteron producing adenomas clinically and radiologically. Our patients was male, he had hypokalemia and hypertension and this findings are appropriate with unilateral hyperplasia cases in literature. We presented this case because of Unilateral adrenal hyperplasia is a rare cause of primary hyperaldosteronism and presented with different findings.

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P239

Clinical case of pituitary apoplexy due to hemorrhagic vasculitis

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Introduction

Pituitary apoplexy is the rare case of panhypopituitarism. We are presenting a clinical case of pituitary apoplexy in a previously healthy 37-year-old woman.

Case report

A 37-year-old woman developed amenorrhea in August 2011. She did not visit a doctor in that time. In December 2011 she suddenly felt severe headache, symptoms of polyuria and polydipsia and temperature of 39 °C. Laboratory results revealed an increased erythrocyte sedimentation rate of 37 mm/h. One month later she felt nausea and vomiting in the morning. She has lost 6 kg of her weight for 2 last months. The cm cystic lesion 1.4×1.5×1.4 was revealed on pituitary MRI. In February 2012 clinical examination in hospital revealed dry skin, acrocyanosis and periorbital pigmentation, BMI 27.1 BP 105/75 mmHg, HR 80 bits/min. Hormone tests revealed panhypopituitarism (cortisol 50 nmol/l (190–650), ACTH – 1.1 pmol/l (0.8–11),TSH 0.9 mU/l (0.2–4.0 mU/l), fT_4 10.0 pmol/l (11–23) and mild hyperprolactinemia (987 mU/l. FSH, LH and IGF1 were normal. Hypotonic poliuria (6 l per 24 h) was found. On repeated MRI the 1.4×0.7×1.4 cm cystic lesion with horizontal level inside it was visualized. On hormonal replacement (cortisone acetate, levothyroxine and desmopressin) she became better, but the complaints for pain in the small joints of the hand and leg swelling appeared. The patient was admitted to the hospital. After clinical evaluation anemia (Hb 72 g/l and ESR 100 mm/h) and acute renal insufficiency (creatinin level 1562 μmol/l and urea 51.4 mmol/l) were diagnosed. Anti-neutrophil cytoplasmic antibody (ANCA) were positive. A diagnosis of ANCA-associated hemorrhagic vasculitis with renal and lungs involvement and pituitary apoplexy related to haemorrhage with resultant hypopituitarism were made. Despite hormonal replacement, haemodialysis and glucocorticoid treatment the patient died from acute cardiac failure on February 2013. On autopsy – pituitary adenoma with hemorrhage revealed.

Conclusion

The following case reports illustrate the rare condition – pituitary apoplexy, with was a first sign of hemorrhagic vasculitis.

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P240

Temporary adrenal failure due to tuberculosis: a rare phenomenon in recent years

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Introduction

Adrenal failure due to tuberculosis is rarely seen nowadays. There are few reports in the literature suggesting that adrenal insufficiency may improve with anti-tuberculosis therapy during the active phase of the disease. Herein, we presented a case of reversible adrenal failure in a patient with active tuberculosis.

Case report

A 50-years-old-female patient admitted to our clinics with the complaints of weakness and darkening of the skin. She had been receiving anti-tuberculosis treatment for the last 8 months. On physical examination, there was hypotension and hyperpigmentation. The laboratory findings were as follows: serum glucose, 72 mg/dl; creatinine, 0.9 mg/dl; sodium, 132 mmol/l; potassium, 4.9 mmol/l; cortisol, 8 μg/dl; and ACTH, 802 pg/ml. In the cosyntropin stimulation test, there wasn't cortisol response (30th min cortisol was 10 μg/dl and 60th min was 11 μg/dl). We started glucocorticoid therapy. In the magnetic resonance imaging, thickness of both adrenal glans were increased. Anti-21 hydroxylase antibody was negative. Anti-tuberculosis treatment were stopped at the 9th month. We repeated the cosyntropin test one month after the therapy was stopped. We detected that there was a positive cortisol response to ACTH (cortisol was 25 μg/dl at the 30th min and 29 μg/dl at the 60th min). We stopped the glucocorticoid since we thought adrenal failure improved.

Conclusion

We suggest that patients who are diagnosed to have adrenal failure due to tuberculosis should be reevaluated after completion of anti-tuberculosis treatment with dynamic tests.

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P241

Malignant feminising adrenal tumor without gynecomastia

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Introduction
Malignant feminizing adrenal tumors are very rare occurring generally in men. The lack of gynecomastia is even rarer in those tumor secreting estrogens alone, or with other adrenal hormones especially cortisol as in the following case.
Case report
A male aged 44, consulted in May 2012 for abdominal pain. Radiological assessment discovered a large tumor measuring 120×95 mm located in the left adrenal with numerous metastases (pulmonary, retroperitoneal and parietal). He was operated on without any hormonal assessment. The pathological examination confirmed the adrenal origin with a Weiss's score =5. Six months later the tumor relapsed and he was operated on again, and then sent to our department for hormonal exploration. Clinical examination showed a skinny man with severe fatigue and anorexia. No sign of Cushing's syndrome was present. There is not any gynecomastia or galactorrhea. Penile size and testicle volume were normal, body heart growth and repartition were normal too. Many parietal nodules were present in the thoracic and abdomen areas. Biological assessment showed high plasma cortisol which failed to be suppressed by dexamethasone (respectively 784.34 nmol/l (50–550) and 4530, high estradiol (E_2)=645.32 pmol/l (<50), high 17OH progesterone=11.7 nmol/l, but low testosterone: 6 nmol/l (10–41)). Radiological exploration showed numerous metastases in the pulmonary, retroperitoneal, and abdominal areas. He died in September 2013 after chemotherapy failure.
Conclusion
Feminizing adrenal tumors are very rare. Gynecomastia which is a classical manifestation may be absent as in this case where metastases were already present at diagnosis. The rapid evolution, severe protein degradation, and breast resistance to E_2 maybe some reasons for the missing gynecomastia.

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P242

Congenital panhipopituitarism and ectopic posterior pituitary

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Introduction
Congenital hypopituitarism may be the result of complications linked with delivery or may sometimes result of insufficient development of the gland in the context of specific genetic abnormalities (PROK2 and PROKR2, LHX4, HESX1, OTX2, GLI2 and SOX3). Interruption or lack of pituitary stalk represents a frequent feature of congenital hypopituitarism.
Case description
We present a patient 39-year-old with congenital panhypopituitarism, mental retardation, dysmorphic syndrome and diabetes type 1 but without diabetes insipidus.
Laboratory findings – baseline tests – have demonstrated combined multiple pituitary hormone deficiency involving GH, TSH, ACTH and GNRH without response to dynamics tests (insulin tolerance test and releasing factors TRH, GnRH and CRH). MRI imaging showed ectopic posterior pituitary at the tuber cinereum level associated with the lack of pituitary stalk.
Medical management consists of replacement therapy for all lines deficient hormones and insulin therapy.
Conclusions
The patients with no visible pituitary stalk on MRI present a more severe form of the disease associated with multiple deficiency of the anterior pituitary hormones, whereas the presence of the pituitary stalk leads to isolated GH deficiency. Follow-up on these patients is necessary, as the natural history of the disease is not established until adulthood.
Keywords
Hypopituitarism, pituitary stalk, ectopic posterior pituitary
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P243

A case report: functioning cystic pheocromocytoma

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Introduction
Cystic adrenal neoplasms are uncommon and were defined with foci of tumor presented in the cyst wall. Adrenal cortical adenoma, adrenal cortical carcinoma and pheocromocytoma may be associated. We report a case of functioning cystic pheocromocytoma.
Case report
A 44-year-old man had abdominal pain on the right side. Abdominal ultrasonography showed a noduler cystic lesion measured 4 cm in diameter with thin septas and thickened wall in the right adrenal. Computed tomography confirmed hypodense lesion with a density of 40 HU. Magnetic resonance imaging supported the diagnosis of cystic adrenal lesion which was not suppressed with fat-suppressed sequence. He had a mild hypertension. As a medical therapy amlodipin and doxazosin were begun for hypertension and preoperative management. Twenty-four-hour urine analysis demonstrated elevated excretion of metanephrine (368.7 μg/day (52–341)), normetanephrine (495.9 μg/day (88–444)) and vanil mandelic acid (46.8 mg/day (1.4–6.5)). Tests were negative for hypercortisolism and primary hyperaldosteronism. Preoperative iodine-123 MIBG SPECT images showed right adrenal lesion accumulation. He underwent a right adrenalectomy with minimal invasive-laparoscopic surgery. Anesthetic induction was performed with fentanyl, propofol, rocuronium and lidocaine. During manuplation of adrenal lesion three hypertensive attacks occurred. Infusion of nitroglycerine, nitroprusside and diltiazem were given to control hypertensive attacks. Postoperative he was normotensive and did not need any replacement therapy. Pathology was cystic benign pheocromocytoma.
Conclusion
Adrenal cysts may be incidental or symptomatic and are classified as pseudocysts, endothelial cysts, epithelial cysts and parasitic cysts. Necrosis or haemorrhage leading to cystic dilatation has been designated to be the pathogenesis of cystsic pheocromocytoma. We report a case of cystic pheocromocytoma who was symptomatic and biochemically functioning.

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P244

Primary adrenal failure due to primary antiphospholipid syndrome

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Introduction
Autoimmune adrenal injury is the most common cause of primary adrenal failure (PAF) (70–90%). Antiphospholipid syndrome (APS) that characterized by thrombosis and abortus may be a reason of PAF. In this presentation we reported a case of primary adrenal failure due to primary antiphospholipid syndrome.
Case
A 34-year-old boy was brought to emergency service due to loss of consciousness. In physical examination patients was confused, blood pressure was 70/50 mmHg, he had widespread hyperpigmentation on his skin and oral mucosa and there was scars in both legs. In Laboratory examination were as follow; blood glucose 37 mg/dl, creatinine 1 mg/dl, sodium 135 mmol/l, potassium 6 mmol/l, thrombocyte count 83 K/ul (140–440), cortisol 1.91 μg/dl and ACTH550 pg/ml. Acute adrenal crisis treatment started and patient hospitalized to evaluate the causes of PAF. Patient was evaluated for possible causes of PAF in terms of HIV, syphilis, disseminated fungal infections and tuberculosis. He had no history for drugs that cause adrenal insufficiency. Bilateral low extremity doppler ultrasound performed due to scars in his legs. Doppler ultrasound revealed thrombosis in bilateral femoral vein, right deep femoral vein, superficial femoral vein, popliteal vein and right vena saphena magna. For thrombosis etiology blood sample were taken for proteinC, proteinS, aPTT and PT%, results were as follow respectively; 85.2% (70–140), 82.4% (60–130), 77.7 sec (20–35), 15 sec (11–16). Antiphospholipid

syndrome was suspected due to increase aPTT levels and thrombosis. Laboratory tests for antiphospholipid antibodies revealed increased anticardiolipin IgG, anticardiolipin IgM and anti β-2 glycoprotein IgG. After 12 weeks repeated test for antiphospholipid antibodies were also high. Due to revised sapporo criteria patient was diagnosed as antiphospholipid syndrome.
Discussion
Antiphospholipid syndrom is characterized with antiphospholipid antibodies. Antiphospholipid antibodies affect coagulation pathway and cause clinical manifestations. APS may affects many organs and one of them is adrenal gland. Adrenal failure in APS is probably related to spontaneous hemorrhagic infarct and adrenal vein thrombosis. Antigens such as lysobiphosphatidic acid in zona fasciculata is target for antiphospholipid antibodies and this is a possible mechanism for adrenal failure in APS. We should keep in mind APS for a possible cause of adrenal insufficiency.

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Catecholamine resistance hypotension after pheochromocytoma resection

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Introduction
Resecting a pheochromocytoma is a high-risk surgical procedure, life threatening complications may occur. In this presentation, we reported a case of resistance hypotension after pheochromocytoma resection.
Case
A 70-year-old male with a history of prostate adenocarcinoma admitted to urology policlinic for cancer screening. Abdominal ultrasound revealed 6.5× 5.5 cm mass in left adrenal gland and patient referred to endocrinology policlinic. He had history of diabetes for 10 years and hypertension. In physical examination blood pressure and pulse were 120/80 mmHg and 75 beats/ min respectively. In laboratory investigations fasting blood glucose was 121 mg/dl, A1C was 9.7%. Plasma renin activity, plasma aldosterone concentration and aldosterone to renin ratio were all normal. 24 h urine metanephrine and normatenephrine were 7053 μg/day (52–341) and 5533 μg/day (88–444) respectively. Surrenal MR detected 6.9×5.2×5.5 cm adenom in right adrenal that enhanced after gadolinium and hyperintens on T2 weighted images. Pheochromocytoma was diagnosed and right surrenalectomy was planned. For premedication patient was hospitalized 10 days before operation. First doxazosin and then metoprolol started. 3 day before operation patients was hydrated with i.v. saline. Preoperative blood pressure and pulse were 120/80 mmHg, 72 beats/min respectively. Intraoperatively short time sodium nitroprusside was used due to hypertensive spell. After removing the mass severe hypotension occurred (60/40 mmHg). Even though administration of i.v. saline, 20 μg/kg per min adrenaline, 15 μ/kg per min noradrenaline, 20 μ/kg per min dopamine and 40 mg prednol, blood pressure did not increase. After 1 h postoperatively blood pressure was 80/40 mmHg. Patient screened in intensive care unit and adrenaline infusion continued for 12 h then blood pressure increased gradually and adrenaline infusion ceased.
Discussion
First line treatment in pheochromocytoma is surgery. Premedication is important to prevent preoperative and postoperative complications. Inadequate premedication may cause hypertensive crisis before resection and severe hypotension after resection. There are many cause for postoperative severe hypotension include residual a-blockade, residual action of vasodilators, inadequate volume replacement and adrenoceptor down-regulation. As a consequence even though adequate premedication severe hypotension may be seen and it should be resistance to catecholamines, in this situation high dose catecholamines or alternative approaches (such as vasopressine infusion) should be used.

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Prepubertal male gynecomastia-issues of diagnosis

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We present the case of 13 years old boy referred to our service in June 2013 for bilateral gynecomastia (appeared for ∼1 year). The boy's father presented delayed puberty (at 18-year-old). No other pathological hereditary conditions were reported.
Clinical examination revealed: gynoid status with height =167 cm (−1.4 DS), weight=63.5 kg, important bilateral gynecomastia with hypo pigmented areola and painful palpation. Sexual development was PII–PIII with testicular volume=4–5 ml and penis dimensions=6–7 cm.
Hormonal profile: testosterone =0.2 ng/ml, FSH=0.876 mUI/ml, LH= 0.119 mUI/ml suggestive for a hypo gonadotrophic hypogonadism or prepubertal status. To differentiate a hypothalamic from a pituitary cause, the LHRH stimulation test was performed. Results revealed FSH and LH levels of 2.00 mUI/ml, 7.17 mUI/ml at 30 min. and levels of FSH=2.04 mUI/ml, LH=5.02 mUI/ml at 45 min suggestive for a hypothalamic hypogonadism. A positive test can also be found in delayed puberty.
Other etiologies of gynecomastia were ruled out by: negative test Barr and normal karyotype analysis (46 XY), normal testicular ultrasound and free β hCG levels, normal thyroid function, prolactin and estradiol levels, as well by the normal hepatic function. We also performed IRM exploration with no hypothalamic or hipophysis lesions.
After 3 months of treatment with tamoxifen the clinical status revealed: H=170 cm, persistent gynecomastia, but normal testicular volume (8 ml) with a normal hormonal profile: testosterone=176 ng/dl, FSH=1.87 mIU/ml, LH=1.07 mIU/ml. The initial hypothesis of hypogonadism was ruled out.
Case particularities
i) A very small number of cases of prepubertal male gynecomastia were reported.
ii) Could the pick of sexual hormones from the LHRH stimulation test triggered puberty?
iii) The normal levels of sexual hormones from the LHRH stimulation test didn't exclude a hypothalamic etiology.

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Spindle cell oncocytoma: a new presentation of a rare disease

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Spindle cell oncocytoma (SCO) is a rare entity with just 18 cases reported in the literature. It was first described in 2002 and was codified as a separate diagnostic entity in the 2007 WHO classification of brain tumours. SCO is a nonadenomatous sellar neoplasm with rich vascularization and intra and supra-sellar infiltration. Usual clinical presentation consists of headache, visual field defects and pan-hypopituitarism. The preoperative diagnosis is difficult due to a lack of specific imaging and clinical findings.
We report the case of a 65-year-old otherwise healthy man who presented with symptoms of visual blurring for 2 months. Clinically he had a bitemporal hemianopsia and imaging investigation revealed an homogenous supra-sellar tumor with 29×23×31 mm which was clearly delimited from the pituitary and molded the optic chiasm. He was admitted to the neurosurgery unit where he was diagnosed with panhypopituitarism: TSH 0.46 mU/l (0.1–4) with FT_4 0.65 (0.93–1.7); LH <0.1 UI/l (1–7), FSH 0.4 UI/l (1–12), total testosterone <10 ng/dl (180–750); ACTH <5 pg/ml (9–50), cortisol 0.4 μg/dl (7–25); IGF1 49.5 ng/ml (75–212) and prolactin 29 ng/ml (9–20). The patient underwent a right frontal craniotomy with partial removal of a highly vascular tumor with difficult cleavage plan from the pituitary.
Histological examination revealed a spindled lesion, with positive immunostain for vimentin, epithelial membrane antigen (EMA), synaptophysin, a Ki 67<1% and a negative immunostain for pituitary hormones.
Postoperatively the patient developed and maintained central diabetes insipidus and had partial visual recovery. The brain MRI performed 6 months after surgery showed a reduction in the tumor volume to 21×19×21 mm and a thin optic chiasm.

The authors present the first described SCO case with only supra sellar presentation. This unique characteristic increased the difficulty of an already challenging preoperative diagnosis and may represent an unknown manifestation of SCO biology.

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P248

A primary adrenal adenomatoid tumor in a young woman

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Adenomatoid tumors are relatively uncommon neoplasms of mesothelial origin, usually occuring in the male and female genital tracts. Rare extragenital adenomatoid tumor has been identified in adrenal gland. The differential diagnosis includes metastatic carcinoma and adrenocortical carcinoma.
We present a case of 30 years old woman with incidentally radiological (ultrasound) finding of unilateral tumor in the right adrenal gland. CT and MRI were of great value in localizing this tumor. The tumor ranged from 5.6 to 6.4 sm in greatest dimension. Clinical and hormonal examinations excluded Sy. Cushing, M. Conn and pheochromocytoma.
She underwent a right adrenalectomy using classic laparatomy. The large tumor (d: 8×7×3 sm) was removed and there were no extra-adrenal extension into periadrenal adipose tissue, infiltration of the adrenal cortex or medulla.
Histologic examination showed numerous cystic spaces lined by flattened of cuboidal epithelial cells. The small cystic spaces are separated by oedematous fibrovascular stroma with rare epitheloid cells with vacuolated cytoplasm.
Immunohistochemical steins were positive for Vimetin(+), s100(+), MCA mesothelial Ag(+), CD 68 (+) and negative for Acitin (−), CK7(−), CD3(−).
Conclusions
Adenomatoid tumor is a rare neoplasm that should be added in the differential diagnosis of any adrenal tumor occurring in adrenal gland. The immunohistochemical profile of this adrenal adenomatoid tumor is very supportive of a mesothelial cell origin.

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P249

Infected giant cystic phaeochromocytoma masquerading as a hepatic abscess

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Introduction
Giant cystic phaeochromocytomas are an exceedingly rare variant of adrenal phaeochromocytomas. We report a case in an 83-year-old lady who initially presented with a swinging pyrexia, initially diagnosed as a hepatic abscess.
Case report
An 83-year-old lady with a history of hypertension was admitted as an emergency with nausea and vomiting, dehydration and rigors. She was pyrexial and dehydrated; pulse 163 and BP 167/86. There were signs of mild congestive cardiac failure. There was fullness in the right abdominal region. Inflammatory markers were elevated. She was treated for intra-abdominal sepsis. CT abdomen revealed a large right liver lobe cystic lesion 12×14 cm. Aspiration followed by a drain was inserted under USS guidance. 1.3 L of blood-stained serous fluid was drained. The patient improved clinically, but following removal of the drain, she relapsed. A further drain was inserted but the repeat CT scan now indicated a partially collapsed mass separate from the liver, and the right adrenal gland could not be visualised. Cyst cultures isolated E. coli that responded to a prolonged course of IV antibiotics. Hydatid ELISA was negative. 24 h urine collection: metanephrines 59.0 μmol/l (<2.0) and normetanephrines 34.6 μmol/l (<4.4); cortisol 328 nmol (50–350). MIBG scintigraphy showed persistent uptake with no evidence of multi-focal disease. Echocardiogram showed moderate LV dysfunction. The patient was initiated on phenoxybenzamine followed by bisoprolol with clinical improvement of her hypertension, tachycardia and cardiac function. She was referred for consideration regarding adrenalectomy. However, it was decided that conservative management with optimised medical treatment was more appropriate.
Conclusions
Large cystic phaeochromocytomas are very rare and may be asymptomatic. As far as we are aware, this is the first report of an infected cystic phaeochromocytoma manifesting as an acute abdomen, and although atypical, should be considered as a differential diagnosis.

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P250

Hyponatremia and diabetes insipidus: a case report

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Introduction
Hyponatremia is defined as a serum sodium level of <135 mEq/l and it is considered severe when the serum level is below 125 mEq/l. In patients with diabetes insipidus treated with desmopressin, it is usually secondary to desmopressin overmedication.
Case report
A 79-year-old man, with a past history of post traumatic central diabetes insipidus treated with desmopressin. The patient had multiple admissions to the hospital due to hyponatremia, that were always associated to overmedication. He went to the emergency room because of asthenia, lethargy, headache, dizziness, nausea, paresthesias, polyuria and polydipsia and denied treatment with higher doses of desmopressin. The baseline endocrine tests revealed severe hyponatremia and hypochloremia with normal levels of potassium, hypercholesterolemia and low normal gonadotropins, total and free testosterone, prolactin, GH and IGF1. The dynamic pituitary reserve test established the diagnosis of panhypopituitarism and the water deprivation test confirmed central diabetes insipidus diagnosis. The magnetic resonance imaging revealed a normal-appearing pituitary gland with no pituitary tumour. The patient was treated with hydrocortisone, levothyroxine and desmopressin, with clinical and laboratory improvement.
Discussion
Although in this case report the most likely etiology to the hyponatremia was desmopressin overmedication, it caused multiple hospital admissions, persisted even after desmopressin dose adjustment and the laboratory tests of those admissions were not suggestive of overmedication. This suggests that other factor might be the cause or at least contributed to this ion change. Besides, the patient presented symptoms compatible with adrenal failure and hypothyroidism and had a head injury history, so other pituitary gland series deficiency might have developed over time. Therefore, panhypopituitarism and other hyponatremia causes must always be excluded in patients with diabetes insipidus, whose hyponatremia persists and is unresponsive to desmopressin dose adjustment.

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P251

Primary hyperthyroidism following successful surgical treatment for secondary hyperthyroidism due to TSH-secreting pituitary adenoma

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Introduction
Secondary hyperthyroidism due to thyrotropin-secreting pituitary adenoma (TSHoma) is rare. Coexistence of TSHoma and primary thyroid disease that could lead to hyperthyroidism is even more unusual.
Case report
A 28-year-old female with longstanding and worsening symptoms of hyperthyroidism was admitted to the hospital. Free-T_4 (32.89 pmol/l) and free-T_3 (6.38 pg/ml) were elevated with moderately increased TSH level (5.997 μIU/ml) suggesting secondary hyperthyroidism. Diagnosis was confirmed by dynamic testing with TRH, that showed no rise in TSH, and MRI revealed a pituitary microadenoma. At the ultrasound thyroid volume was normal, with no nodules nor enhanced blood flow, but with decreased echogenicity and heterogeneous echotexture. Antithyroid antibodies were negative and 24 h iodine uptake was increased (76%). Somatostatin analogue, administered before transsphenoidal neurosurgery, resulted in a moderate improvement of symptoms

and hormonal results. After successful tumour removal clinical and laboratory signs of hyperthyroidism resolved. However, a month after neurosurgery symptoms of thyrotoxicosis recurred with elevated fT_4:32.94 pmol/l, fT_3:10.17 - pg/ml and suppressed TSH $<$ 0.001 μIU/ml. No eye signs, neck pain or goiter were present. Iodine uptake was low (3.5%) and thyroid was hypervascular and remarkably hypoechoic at ultrasound. TPO-ab (91.2 IU/ml) and TG-ab (10.11 IU/ml) titers increased but TR-ab were negative. We diagnosed iodine-induced hyperthyroidism in a patient with preexisting silent thyroid disease (autoimmune thyroiditis) in whom povidone-iodine antiseptic solution was used during neurosurgery. Patient was treated with thiamazole and prednisone with a prompt improvement. Five months after surgery she was well, euthyroid, with no residual adenoma on MRI and a normal response of TSH secretion in TRH test (TSH 0':1.24 μIU/ml, 60':7.66 μIU/ml).
Conclusions
Exposure to topical iodine-containing solutions could lead to iodine-induced thyroid dysfunction in susceptible patients with preexisting thyroid disease. In such patients with coexisting pituitary adenomas usage of iodine-based antiseptic solutions should be avoided.

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P252

A case of addison's disease associated with ankylosing spondylitis

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Addison's disease (AD), is an autoimmune disorder. However, its association with connective tissue diseases is rare. Here, we report a case of AD associated with ankylosing spondylitis (AS).
Case
A 57-year-old male patient admitted to internal medicine polyclinic with complaints of debility and anorexia. In the physical examination, he has hyperpigmentation on his skin, gingiva and palm lines. Blood pressure was 80/50 mmHg, pulse was 64/min. The other examination data were normal. Laboratory examination revealed potassium level as 9.3 mmol/l. Within his other laboratory examination, glucose was 61 mg/dl, urea was 68.5 mg/dl, creatin was 1.6 mg/dl, sodium was 133 mmol/l. After urgent intervention for the hyperpotasemia, he transferred to Endocrinology with a diagnosis of adrenal insufficiency. His cortizol level was 2 mg/dl. Hydrocortizone was given as treatment. In few days, patient's debility rapidly got better. His blood pressure, glucose and K levels improved. In the repeated examination, patient's kyphosis was noticed. He described progressive kyphosis since years and morning stiffness lasts about half an hour and relieved with movement. In rheumatology examination, sacroiliac sensitivity was positive, tragus-wall distance was 25 cm, occiput-wall distance was 19 cm, chest expansion was 2 cm, Schober test was 0.8 cm, modified Schober was 1 cm, right lateral expansion was 8 cm, left lateral expansion was 6 cm and intermalleolar distance was 69 cm. Sacroiliac and vertebra X-ray revealed stage four bilateral sacroileitis with bamboo spine and syndesmophytes presence. Ophthalmology examination was normal. He was diagnosed as AS and AD.
Discussion
AD has a prevalance of 4–11/100 000. AD may develop due to a number of causes, however autoimmunity has become the main cause now. We report a case of AD associated with AS and aimed to take attention about coexistence of AD and other autoimmune disorders such as connective tissue diaseases.

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P253

A case report: posterior pituitary evaluated as microadenoma in the magnetic resonance imaging

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Introduction
Posterior pituitary appears hyperintense in T1 series in the sagittal section of magnetic resonance imaging. We report a case whose posterior pituitary magnetic resonance images could be evaluated as microadenoma.
Case report
A 20-year-old woman evaluated in Gynecology for oligomenorrhae. Serum prolactin was 27 ng/dl. Magnetic resonance imaging of pituitary showed a nodular lesion in the left measured 3 mm in diameter and hyperintense in T2 series which could not be distinguished from artifactial lesion. She was referred to Endocrinology. Pituitary hormonal function was normal. We decided to follow-up. After three months magnetic resonance imaging of pituitary showed a nodular lesion in the posterior of the left measured 6 mm in diameter and hyperintense in T1 series. The lesion was taking more contrast than adenoma and was not like cystic lesion that was hypointense in T1 series. The appearance of the lesion could be interfered with fat tissue, sphenoid bone or partial volume artifact.
The fat-suppressed images were taken. There was no contour lobulation of pituitary and there was no change with dynamic series. The lesion was not observed in the posterior. We took axial section and evaluated the lesion as posterior pituitary.
Conclusion
We report a case of posterior pituitary which was asymmetric and thickened and localized in the left parasagittal section. This localization caused pseudonodular appearance in the middle when surrounded with normal pituitary.
Pituiary microadenoma can be suspicious. Some anatomical variations contribute to these images. Patients may have unnecessary evaluation for a long period.

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P254

Acromegaly accidentally diagnosed: a typical course of the disease

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Introduction
Acromegaly is a rare endocrinopathy which shows characteristic phenotypic and metabolic features. Primarily patients in their forties or fifties suffer from this disorder but the main problem is late diagnosis, especially in men, even 10 years after the first symptoms. We present an unusual clinical course of acromegaly with no phenotypic features to stress the need to perform complete evaluation of endocrine function in hypogonadal patients.
Case report
A 24-year-old male was admitted to the Department of Endocrinology of the Medical University of Lublin in order to confirm the diagnosis of hypogonadism established in an outpatient clinic. The patient complained about low libido, erectile dysfunction, excessive sweating at night present for 8 months. The course of pubescence was normal. Physical examination showed normal genitalia, scraggly facial hair, normal inguinal and pubic hair. Hormonal tests of the hypothalamic–pituitary system showed hypogonadotrophic hypogonadism, hyperprolactinemia and surprising hypersomatotropism (IGF1: 814.3 ng/ml + GH: 25.10 ng/ml) which was confirmed in the OGTT (75 g): GH 0': 21.3, 60′: 18.4 ng/ml. In the differential diagnosis the patient was preliminary diagnosed with acromegaly, which was confirmed with MRI that showed pituitary macroadenoma 30 × 35 × 20 mm in size, with sphenoid sinus and left cavernous sinus expansion and optic chiasm compression and modeling. The patient was qualified for transsphenoidal adenectomy preceded by 6 months of treatment with long-acting somatostatin analogue. The surgery was uncomplicated. The patient's hormone levels returned to normal.
Conclusions
In differential diagnosis of hypogonadism growth hormone-secreting pituitary adenomas with abnormal clinical course should be considered.

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P255

Diabetes insipidus as the primary symptom of infundibuloma

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Introduction
Neurohormonal diabetes insipidus (DI) is a rare disorder caused by partial or total vasopressin deficiency which results in diluted urine characterized by polyuria

and polydipsia. In 30–50% of the cases the cause of the disease is unknown; it is the so-called idiopathic diabetes insipidus. Other causes include: tumors of the CNS most commonly craniopharyngioma, pituitary macroadenomas, central nervous system trauma, inflammatory state of hypothalamus or pituitary gland, CNS surgery, congenital organic diseases or genetic defects. The treatment includes long-action vasopressin analogues. We present the similarity of the clinical course of infundibuloma irrespective of the patient's gender.
Case report
A 39-year-old male perfectly mentally and physically healthy three years ago diagnosed with central diabetes insipidus with focal lesion 5×5 mm in size, confined to the pituitary stalk supporting optic chiasm and characteristic of DI low signal intensity on T1-weighted MR images of the nerves. The field of vision was normal. After a year the patient presented symptoms of hypogonadism (hypogonadotrophic hypogonadism), which required additional replacement treatment with desmopressin and parenteral testosterone with a good clinical result.
A 42-year-old female with central diabetes insipidus diagnosed at the age of 33 caused by thickening pituitary stalk to 5 mm with no accompanying symptoms. After a year of replacement therapy with desmopressin appeared the symptoms of hypogonadism in the form of secondary amenorrhea at the age of 34.
Conclusions
The primary clinical symptom of infundibuloma is diabetes insipidus followed by hypopituitarism in the course of which the gonadotrophic axis defect prevails irrespective of the patient's gender.
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P256

An unusual case of reversible empty sella
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A 22-year-old female complaining about irregular menses associated to a slight increase of serum PRL and the recent onset of headache, nausea, dizziness, photophobia, occasional diplopia, visual impairment, anxiety and panic attacks was evaluated for the possible presence of a cerebral mass with intracranial hypertension. Fundoscopic examination and visual field were both normal. There was an empty sella with a flattened pituitary gland along the floor of the pituitary fossa and normal ventricular size at NMR. A lumbar puncture showed an increased CSF opening pressure (250 mmH_2O), with normal composition of CSF. FSH, LH, 17β estradiol, FT_4, FT_3, ACTH and cortisol were normal. PRL and TSH were slightly augmented whereas IGF1 and the GH response to GHRH + arginine were reduced. Clinical conditions slightly improved and the patient was discharged with 12.5 μg of levo-tiroxine. After 3 months, she came back complaining about the progressive worsening of the headache and the onset of cervical pain, with scarce response to analgesics, a further worsening in orthostatic position and transient relief after prolonged bed rest and hydration. At NMR the empty sella was no longer evident as the pituitary gland had reassumed its normal position. The peduncle was dislocated on the right side with no evidence of a pituitary adenoma. Cerebellar tonsils were displaced in the occipital foramen and there was an impregnation of the dura mater and of the meninges of the internal acoustic meatus. The picture was that of a CSF hypotension, probably determined by the previously performed lumbar puncture causing a meningeal leak of CSF, with consequent desappearance of the empty sella. The patient was submitted to epidural blood patch at lumbar level. The clinical as well as the NMR picture gradually improved.
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Acromegaly with a normal pituitary gland
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Background
Acromegaly most commonly results from an excess production of GH and secondary increase in IGF1. More than 95% of the time from the pituitary gland, but the source of excess GH secretion may not necessarily be pituitary in origin. Ectopic acromegaly may arise due to neuroendocrine tumors by production of GHRH and in <0.5% of the cases from ectopic pituitary remnants in the sphenoid sinus.
Clinical case
We present a case of a 37 years old man with typical symptoms of acromegaly. Initial laboratory evaluation consistent with the diagnosis of acromegaly, hGH = 2.699 ng/ml (0.014–1.406 ng/ml) and IGF1 = 956.00 ng/ml (109–284 ng/ml), prolactin and TSH levels were normal. A brain MRI with special attention to pituitary gland revealed normal size and configuration with no definitive lesions identified. However, a large heterogeneous mass involving the sphenoid sinus extending into the posterior ethmoidal air cells was seen. Patient underwent transphenoidal surgery. Immunostaining analysis of the sphenoidal mass revealed; GH(+), prolactin(+), TSH(+), ACTH(−), FSH(−), and LH(+). Post-surgical evaluation showed persistent levels of GH and IGF1 (hGH = 1.413 ng/ml and IGF1 = 802 ng/ml), and no glucose suppression after an oral glucose tolerance test. After surgery MRI showed normal size pituitary gland but residual heterogeneous material involving the sphenoidal sinus. Due to the persistence of biochemical and radiological abnormalities patient required Gamma-knife treatment and medical therapy with Cabergoline and Sandostatin.
Conclusion
In patients with clinically and biochemical evidence of acromegaly but with normal findings in the pituitary gland, ectopic origin due to embryological pituitary remnants should be consider. Ectopic acromegaly is a very rare clinical presentation. Lack of consideration of this etiology could be responsible for failed TES in endocrinologically active tumors.
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Different courses of Carpenter syndrome
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Introduction
Autoimmune polyglandular syndrome type 2 (APS type 2) is co-occurrence of primary adrenal insufficiency (Addison disease) and autoimmune thyroid disease – most commonly Hashimoto thyroiditis (Schmidt syndrome). If it is associated with type 1 diabetes mellitus it is known as Carpenter syndrome. We present clinical pictures of two 33-year-old patients (born in 1980) diagnosed with APS type 2 manifested as Carpenter syndrome to emphasize different courses of the disease.
Case report
A 33-year-old male diagnosed with diabetes type 1 at the age of 19, treated with intensive insulin therapy (currently Lispro + Glargine), at 22 presented with hypothyroidism in the course of autoimmunological thyroiditis required replacement therapy with levothyroxine. The patient was metabolically balanced until 2007 (HbA1c < 6.5%), but at the age of 27 among severe symptoms of adrenal crisis he was diagnosed with primary hypoadrenalism. The patient received a typical replacement therapy (Hydrocortisone + Cortineff) but has not attained metabolic balance (HbA1c chronically >7%). Additionally, the subject was diagnosed with vitiligo.
A 33-year-old male diagnosed with diabetes type 1 at the age of six, treated with intensive insulin therapy (currently Glulisine + Glargine), additionally at 24 diagnosed with Addison disease, which required replacement therapy (Hydrocortisone + Cortineff), whereas when 33 the patient developed another endocrinopathy, i.e. hyperthyroidism in the course of Graves disease. Currently, the patient is undergoing a thyreostatic therapy. Coinciding endocrinopathies did not result in worsening of metabolic balance (HbA1c chronically <6.5%).
Conclusions
Coinciding endocrinopathies in the course of Carpenter syndrome require careful and prompt diagnosis as the types of endocrinopathies and their course may not be anticipated on the basis of the patient's age. Hormonal replacement therapy must be individually adjusted to the specific coincidence of endocrinopathies in the course of APS type 2 manifested as Carpenter syndrome.
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Anterior pituitary insufficiency and spontaneous fertility: case report

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Introduction
The reversibility of idiopathic hypogonadotropic hypogonadism (IHH) is well documented and may result in spontaneous fertility (SF). These facts are little discussed in multiple anterior pituitary insufficiency. We describe a case report of this disease with SF after androgen therapy withdrawal.
Case report
A 7-year-old boy was referenced due to short stature. Auxology: height 108 cm (−2.86SD); predicted adult stature (PAS) 169.5 cm (−0.78SD); growth velocity 2 cm/year; bone age 6 years (−2.82SD). Past history of traumatic delivery. Cranial-CT revealed intrasellar arachnoidocele. Laboratory: partial gonadotropin and ACTH insufficiency and total GH and TSH deficiency. Somatropin, levothyroxine and hydrocortisone (SOS) therapies were initiated. At the age of 12: Tanner scale P1G2; testicular volume (TV) 6 ml. Three years later he showed same Tanner stages. Puberty induction (PI) with testosterone enanthate (TE) was performed. At the age of 19 he stopped somatropin. He reached final height 180.9 cm (exceeded PAS), Tanner P2G4 and TV 10–15 ml. Reassessment after somatropin withdrawal: IGF1 85 ng/ml (116–358), displaying persistence of GH deficit. Revaluation with Cranial MRI: pituitary hypoplasia, thin stalk and ectopic neurohypophysis; negative PROP1 mutation.
He stopped TE at the age of 29 with intention to become a father. SF occurred 4 months later. Spermogram: normoasthenozoospermia, total testosterone 1.7 ng/ml (2.7–11.0). Eight months after testosterone withdrawal he presented with clinical and laboratory androgen insufficiency and he restarted ET. Currently, he's clinically stable, father of a 2-years-old child, with normal psychomotor development.
Conclusions
Reversibility of hypogonadism and SF chance should be considered in all patients with IHH and anterior pituitary insufficiency.
In this case, we admit that TE withdrawal has contributed to a partial reactivation of the hypothalamic–pituitary–gonadal axis, sufficient to stimulate spermatogenesis. A TV of 6 ml at age of 12 (and 10–15 ml after PI) can be a predictor of greater chances of SF (it indicates some endogenous gonadotropin production).

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P260

Hyporeninemic hypoaldosteronism with severe hyperkalemia following adrenalectomy for primary hyperaldosteronism : a case report

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Background
Post-adrenalectomy persistent hyperkalemia, that lasts >3 months and needs to be treated, is a potentially serious, but not apprehensively investigated complication after surgical treatment in patients with aldosterone-producing adenomas (APA).
Case report
A 53-year-old male presented type 2 diabetes mellitus and a 10-year history of resistant hypertension requiring multidrug treatment with antihypertensives of eight different classes. Primary aldosteronism with non-suppressive serum aldosterone (0.43..0.32 nmol/l, normal value <0.28 nmol/l) was confirmed in a standard saline infusion test. MRI scan revealed a left-sided adrenal mass (21× 30 mm). Adrenal vein sampling confirmed left-sided unilateral hypersecretion of aldosterone. Patient underwent an uneventful left adrenalectomy, following which decrease of blood pressure was observed. Two months after surgery patient presented with hyperkalemia (6.25 mmol/l, normal value 3.6–5.3 mmol/l). His aldosterone (0.03 nmol/l, normal value 0.08–1.11 nmol/l) and renin levels (4.1 mIU/l, normal value 4.4–46.1 mIU/l) were inappropriately low, suggesting hyporeninemic hypoaldosteronism.
Discussion
Post-operative hypoaldosteronism is well documented in unilateral adrenalectomy for APA. It is related to a decrease in adrenal mass, or a transient supression of the contralateral gland via suppressed plasma renin levels, impairing renal K^+ clearance and consequent hyperkalemia. In most cases, hyperkalemia is only transient, occurs only once during the first months after adrenalectomy and resumes spontaneously without intervention. Male sex, older age, longer duration of hypertension, lower nadir serum K^+ and already preoperative impaired renal function are identified as the most important factors of post-adrenalectomy hyperkalemia.
Conclusion
When persistent hyperkalemia is detected, mineralocorticoid replacement treatment, with a low-potassium and high-sodium diet should be initiated. Drugs that may have prevented adequate recovery of renin–aldosterone axis should be stopped. Endocrinologists should be aware of this complication and should closely monitor K^+ levels and renal function after adrenalectomy indicated for APA.

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Clinical case reports – Thyroid/Others

P261

A new mutation associated with pseudohypoparathyroidism? two case reports

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We describe the clinical case of two childbearing age women with thyroid dysfunction, hypocalcemia, hyperphosphatemia, and high levels of PTH.
Case 1
A 34-year-old woman with infertility for 3 years, microprolactinoma treated with low-dose dopamine agonists, autoimmune primary hypothyroidism and obesity. She had irregular menstrual cycles and fatigue. Weight 130 kg, height 155 cm, cervical acanthosis nigricans and round face. Calcium 6.6 mg/dl, phosphorous 4.9 mg/dl, PTH 244 pg/ml and vitamin D 15 ng/ml.
Case 2
A 40-year-old woman from Nepal with mild osteopenia, subclinical hypothyroidism and hospitalization for severe hypocalcemia and tetany in 2003. She was asymptomatic under treatment with calcium and vitamin D. Weight 63 kg, height 154 cm and brachydactyly of the 5th finger of hand. Calcium 6.3 mg/dl, PTH 546 pg/ml and vitamin D 37 ng/ml at the diagnosis. In both cases, genetic study showed no mutations in the GNAS gene. However, two polymorphisms in heterozygosis, with no clinical relevance to date, was found: case 1 c.393C >T(p.Ile131Ile) and c.1038+55T>C(IVS12+155), and case 2 c.393C >T(p.Ile131Ile) and c.586-42G>A (IVS7-42).
Conclusion
We describe two suspected cases of pseudohypoparathyroidism (PHP) type 1a or 1c with negative genetic test for mutations in the GNAS gene but with a common polymorphism in heterozygosis. No GNAS gene mutations are detected in 30–40% of PHP so many of their molecular mechanisms are not known. We think that polymorphism c.393C>T(p.Ile131Ile) could be a new mutation related to PHP.

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P262

Prevalence of thyroid abnormalities among psoriatic patients

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Introduction
Psoriasis is not only a skin disease, is a chronic inflammatory disease associated with serious comorbidities: psoriatic arthritis, metabolic syndrome (obesity, dyslipidemia and insulin resistance), Crohn's disease, depression, ocular problems, cardio-vascular diseases (myocardial infarction), cancer.
Methods
1236 patients (male 54.13% and female 45.87%) with psoriasis were seen in an Outpatient Clinic over a period of 8 years (2004–2011). The presence of different concomitant diseases were noted within psoriasis patients (Table 1).
Results
Comorbidities were absent in 732 patients (59.22%) and present in 504 patients (41.78%); cardio-vascular diseases in 162 patients (12.52%), diabetes in 50 cases (4.03%), psoriatic arthritis in 166 patients (13.43%).
Thyroid problems were present in 22 patients representing 1.77% of all cases (autoimmune thyroiditis one patient/0.08%, thyroidectomy eight patients/0.64%, hypothyroidism nine patients/0.73%, thyroid goiter three patients/0.24% and thyroid cancer one patient/0.08%).

Table 1 Concomitant diseases in psoriasis patients

Autoimmune thyroiditis	1	0.08%
Tyroidectom	8	0.64%
Hypothyroidism	9	0.73%
Thyroid goiter	3	0.24%
Thyroid cancer	1	0.08%
Total	22	1.77%

Conclusions
In our study, we didn't observe a statistical importance of prevalence of thyroid abnormalities within patients with psoriasis.

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Coexisting hurthle cell neoplasm and thyroid hormone resistance

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Introduction
Resistance to thyroid hormone (RTH) is an inherited syndrome characterized by reduced responsiveness of target tissues to thyroid hormone (TH). It is characterized by high serum concentrations of free T_4 (Ft_4) and usually free T_3 (Ft_3) accompanied by normal or slightly high serum TSH concentrations. When RTH is suspected, the diagnosis should be confirmed by direct sequencing of the TR-β gene to identify mutations. Hurthle cell neoplasm (HCN) accounts for only about 3–10% of all differentiated thyroid cancers. To our knowledge; there isn't any case reporting coexistence of HCN and RTH; so whe want to present this case.
Case report
A 38-year-old man presented with palpable goiter, tachycardia, nervousness, dysphagia and dyspnea. Thyroid function tests demonstrated a normal serum TSH of 1.21 μIU/ml but elevated fT_3 of 6.00 pg\ml and fT_4 of 2.44 ng\dl. He had normal α-subunit and partially suppressed TSH level by administration of incremental doses of L-T_3, and positive TSH response to TRH stimulation. Genetical testing was ordered to confirm diagnosis. His thyroid ultrasound showed hypoechoic nodule measuring 24×18×34 mm. FNAB of the nodule was compatible with folliculer neoplasm. Histopathological examination after total thyroidectomy revealed HCN with a focus of 20 mm in the long diameter at the nodule location, showing capsular invasion. Radioiodine ablation (RA) was planned.Waiting for RA, he was treated with 300 mcq L-T_4 and his TSH did not suppress, which will be also an important problem during the treatment and follow-up of HCN. The suppression of TSH could be difficult when HCN coexists with RTH. Increasing the dose of L-T_4 can result in thyrotoxicosis without TSH suppression.
Conclusion
In conclusion, this is the first case of reporting coexistance of HCN and RTH; management is more challenging.

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Primary hyperparathyroidism with severe hypercalcemia during pregnancy

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Introduction
Primary hyperparathyroidism (PHPT) commonly goes unrecognized due to the physiological changes of pregnancy.PHPT is associated with significant maternal and fetal morbidity and mortality. Current evidence supports parathyroidectomy is the main treatment, performed preferably during the second trimester, when the serum calcium is above 11–mg/dl. We report the clinical course of a woman with newly diagnosed gestational PHPT who refused minimally invasive parathyroidectomy during and after pregnancy.
Case presentation
A 23-year-old primigravida woman presented during her 35th week of gestation with a 2 day history of severe nausea and vomiting. She denied any history of abdominal pain, constipation, polydipsia, polyuria, weight loss, muscle weakness. She had no history of calcium disorders, kidney stones, fractures, osteoporosis. She was not taking any drugs which could influence her calcium status. Admission laboratory tests revealed several hypercalcemia with a adjusted calcium level 18.43 mg/dl, phosphorus 2.39 mg\dl and parathyroid hormone (PTH) 775 pg/ml serum alkaline phosphatase (ALP) 157 IU/l urinary calcium level 503 mg/24-h Ultrasound examination of her neck identified one suspicious parathyroid enlargement at the inferior pole of thyroid gland measuring 17×13×11 mm. Severe hypercalcemia was treated with i.v. saline infusion, caciitonin, diuretic and corticosteroids. She denied minimally invasive parathyroidectomy during third trimester. When her serum calcium level dropped the level of 13.5 mg\dl, cesaran section was performed. The baby was healthy and normocalcemic with a calcium level of 9.8–mg/dl and a PTH level of 121 pg/ml on day 1. After pregnancy she again refused parathyroidectomy and medical treatment and the mother and baby were discharged home on the six day after delivery.
Conclusions
Timely recognition and effective management of PHP in pregnancy is important because it represents a preventable cause of fetal and maternal morbidity and mortality.Although our case lately presented, both maternal and fetal outcomes was excellent with medical intervention.

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P265

Acute necrotizing pancreatitis as first manifestation of primary hyperparathyroidism

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We present a case report of a young female patient with hypercalcemia-induced acute necrotizing pancreatitis as first manifestation of a benign parathyroid adenoma.
Case
A 46-year-old female presented at the emergency room with a sudden attack of severe epigastric pain and vomiting. Clinical examination revealed a severely ill patient, a silent abdomen which was distended with painful percussion and palpation of the epigastrium. Blood analysis showed signs of inflammation. Serum amylase was 754 U/l (24–72 U/l) and serum lipase was 7189 U/l

(13–300 U/l). Serum calcium was increased to 13.3 mg/dl. Based on the clinical picture and blood analysis she was diagnosed with acute pancreatitis. Abdominal ultrasound was carried out and showed no evidence of cholelithiasis or dilated bile ducts. Abdominal CT scan showed the development of pancreatic pseudocysts and necrosis of the pancreas with few remnants of normal pancreatic tissue. The patient was treated conservatively with intravenous fluids and analgesia. After that broad spectrum antibiotics was started because of recurrent episodes of fever and abdominal pain. Serum levels of intact parathyroid hormone (iPTH) were determined and showed an increase up to 273 pg/ml (13–54 pg/ml). This result confirmed hypercalcemia caused by hyperparathyroidism. Ultrasound of the parathyroid glands showed tumor adjacent to the left thyroid lobe. The patient underwent surgical resection of this tumor, and histological examination confirmed the diagnosis of benign parathyroid adenoma. After that surgical cystogastrostomy and necrosectomy of the pancreatic corpus was performed. She recovered well and the patient remained free of symptoms without signs of exocrine or endocrine pancreas insufficiency.
Result
Good cooperation between gastroenterologists, endocrinologists and surgeons is important in treating this rare phenomenon of acute necrotizing pancreatitis caused by PHPT induced hypercalcemia.

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P266

Is repeated fine needle aspiration expedient when the first one is nondiagnostic

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Background
It is disputable whether to repeat FNAB after the first one was nondiagnostic, or to submit the patient to operation.
Methods
Indication for FNAB was a thyroid nodule of ≥ 1 cm or of a less size with clinical or ultrasound features of malignancy. In case of multinodular goiter each nodule was punctured and examined separately.
3929 cases (8%) were noninformative out of 49 419 FNAB of thyroid nodules performed in North-West Regional Endocrine Center during 2010–2012 years. Among these technical mistakes occurred in 69 cases (1.7%), and insufficient amount of follicular epithelial cells was in 3861 (98.3%) of cases. Repeated FNABs were performed to all patients with nondiagnostic primary results of FNAB in 1 month after the first one. During the second FNAB, we took cell material into four glasses instead of two glasses like for the first time.
Results
3760 (96%) of cases became informative after repeated FNAB. 168 cases remained nondiagnostic. Malignant tumours were revealed in 1.8% of cases of repeated FNAB, that is significantly lower than among primary FNAB (3%).
Conclusion
The results of the study show that repeated FNAB is very valuable diagnostic procedure, that allows to transfer the majority of nondiagnostic FNAB into group suitable for diagnostics.

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P267

Analysis of 40 696 FNAB of thyroid nodules performed in one center

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Background
Fine needle aspiration biopsy is generally acknowledged as a «gold standard» for diagnostics of thyroid malignancies. However, data on FNAB vary considerably in publications from different centers. In this study we have analyzed the results of more than 40 000 FNAB of thyroid nodules performed in North-West Regional Endocrine Center during 2010–2012 years.
Subjects and methods
Indication for FNAB was a thyroid nodule of ≥ 1 cm, and a nodule < 1 cm with clinical and ultrasound signs suspicious for malignancy. In case of multinodular goiter each nodule was examined separately. Female-male ratio was 10:1. Mean age for women was 56.0 ± 13.7 years, for men – 54.7 ± 14.8 years.
Results
Cytological results were as follows according to the Bethesda system: noninformative – 8%, benign nodules – 81.9% (colloid nodules 71.6%, Hashimoto's thyroditis – 10.2%, subacute thyroditis and others – 0.02%), follicular lesion – 7.2% (follicular neoplasm – 7.1%, follicular lesion of inderterminate significance – 0.1%), suspicious for malignancy – 0.02%; malignant tumours – 3%, among the latter 93.0% were papillary carcinomas.
Conclusion
The presented results based on analysis of more than 40 000 FNAB confirm that this method is highly informative in detection of thyroid malignancies. Application of FNAB significantly increases number of patients submitted to surgery due to a malignant tumour, and decreases quantity of diagnostic operations. Only 12.5% operations in 2004 were performed in our clinics in patients with malignancies but in 2012 its percentage increases up to 53%.

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P268

Functional results of inadvertent parathyroid excision during thyroid surgery

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Background
Unintented parathyroidectomy during thyroid surgery – is one of typical complications, especially when an operation is augmented by lymphodissection. In this work, we present the results of calcium metabolism analysis in such patients.
Subjects and methods
3929 operations of patients with different thyroid diseases were performed during 2010–2012 years. 82 inadvertently excised parathyroid glands were revealed at histological examination (2.1% of all thyroid surgeries). We followed up serum calcium level each month in this group of patients.
Results
Out of 82 patients 24 (29.3%) had follicular adenomas at histological examination, 46 (56.1%) – papillary carcinomas, 2 (2.4%) – medullary carcinomas, 3 (3.7%) – follicular carcinomas, 7 (8.5%) – diffuse toxic goiter. Lobectomies were performed in 19 (23.2%) patients, thyroidectomies in 59 (71.9%) patients, central lymphodissections in 4 (6.1%) patients. One parathyroid gland was unintentionally excised in 77 (93.9%) of cases, two glands – in 5 (6.1%) cases. Postoperative hypocalcemia appeared in 33 (40.2%) patients and it lasts more than 6 months in 15 (18.2%) patients.
Conclusions
These results suggest that parathyroid injury during thyroid surgery remains a serious problem, and hypocalcemia may develop even if one parathyroid gland is excised.

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P269

Scleredema diabeticorum in a nonregulated type 2 diabetic patient

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Scleredema diabeticorum is an infrequently seen connective tissue disorder that effects upper part of the body. The affected skin is thick, hard and painless. A 51-year-old male Type 2 diabetic patient was referred to our department for infected foot ulcer. On physical examination erythematous, hard, painless, wide-reaching skin lesion on his upper back and shoulders except from draining

diabetic foot ulcer on his right foot first and second fingers. Multipl subcutanously insulin therapy was started because of poor regulated diabetes and intravenously antibiotherapy was performed to the patient because of infected diabetic foot ulcer. A biopsy was done to the lesion to distinguish scleredema.

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P270

Rare coexistence of familial mediterranean fever and familial partial lipodystrophy: presented as acute pancreatitis due to severe hypertriglyceridemia

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A 21-year-old female (height: 148 cm, weight: 38 kg, and BMI: 17) was referred to our endocrinology outpatient polyclinic with the complaints of severe abdominal pain and severe hypertriglyceridemia. The patient's medical history revealed diabetes and FMF. Physical examination revealed a marked loss of subcutaneous fat from the extremities leading to prominence of muscular contours and veins, with excess fat around the face, submental and dorsocervical region. Despite the technical limitations which hindered us making diagnosis of FPLD1, the metabolic profile, existence of type 2 diabetes, hepatic steatosis and lack of subcutaneous fat and cushingoid appearence were consistent with FPLD1.

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P271

Localized Aspergillus thyroiditis in patients with diabetic nephropathy

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Aspergillosis is a major problem in immunosupressed patients. We report a 65-year-old male patient with chronic renal failure (CRF) due to diabetic nephropathy who had arthralgy, malaise and high C-reactive protein level. Chest computed tomography revealed that thyroid nodule in the left thyroid lobe. Fine-needle aspiration biopsy of the thyroid revelead thyroidal invasion of Aspergillus. High-resolution computed tomograghy (HRCT) of the chest showed no evidence of intrapulmonary fungal lesions. We started voriconazole treatment. After treatment with voriconazole, clinical and laboratory improvement was seen.

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P272

Drug-induced syndrome of inappropriate antidiuretic hormone secretion

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Introduction
Hyponatraemia is one of the most common electrolyte abnormalities that may be drug-induced either as a result of inappropriate antidiuretic hormone secretion (SIADH) or excessive sodium loss. SIADH is diagnosed on the basis of low plasma osmolarity associated with inappropriately concentrated urine.
Case report
A 67-year-old woman was admitted to hospital because of progressive confusion and perseveration. Her medical history included bipolar disorder, arterial hypertension and gastritis. Her drug therapy on admission was chlorpromazine (Prazine), sertaline (Zoloft), fluphenazine (Moditen), lisinopril (Laaven), and pantoprazole (Controloc). On physical examination the patient appeared euvolemic without evidence of congestion or dehydration. The CT scan of the brain and chest X-ray were normal. Laboratory tests revealed severe hyponatraemia (111 mmol/l) and the infusion of a 3% saline was administered. Approximately 24 h after admission the patient's serum sodium increased to 120 mmol/l and her mental status improved. Hyponatraemia, low serum osmolarity (258 mOsm/kg), high urine osmolarity (398 mOsm/kg), high urine sodium (64 mmol/l) together with normal renal, thyroid and adrenal function, all supported diagnosis of SIADH. Therefore, fluid restriction was instituted and her chronic drug therapy suspended. Serum sodium level increased progressively and low doses of new psychotropics re-initiated (risperidone and escitalopram). At the time of hospital discharge, serum sodium level was 133 mmol/l. A follow-up serum sodium 3 weeks after discharge was within the limits of normal range.
Conclusion
Effective clinical management of drug-induced hyponatraemia can be handled through understanding of the underlying pathophysiologic mechanisms and awareness of the adverse effects of certain pharmaceutical compounds on serum sodium levels.

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P273

Heparin-induced hyperkalaemia in a patient with type 2 diabetes: a case report

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Introduction
Heparin is extensively used amongst different medical and surgical specialities for prophylaxis and treatment of venous thromboembolism and suspected coronary syndromes. Hyperkalaemia is known to occur as an effect of heparin treatment through its action on the renin-angiotensin system, especially when used at treatment doses. Hyperkalaemia is a serious electrolyte disturbance, which may precipitate potentially fatal cardiac arrhythmias. We describe a case of a patient developing hyperkalaemia secondary to a prophylactic dose of low-molecular weight heparin.
Case report
A 65-year-old man with ischaemic heart disease, type 2 diabetes and peripheral vascular disease was admitted under the vascular surgical team with ischaemic right leg. He was commenced on prophylactic low-molecular weight heparin. Four days into his hospital stay he became hyperkalaemic with serum potassium of 6.1 mmol/l (normal 4.5–5.3 mmol/l). The potassium level remained persistently elevated in spite of stopping the ACE inhibitor and spironolactone, which he was on for several years. He responded only briefly to insulin–dextrose infusions. The hyperkalaemia resolved gradually on discontinuing the prophylactic heparin.
Discussion
Compared to normal population, hyperkalaemia is more prevalent among diabetics. Hyperglycaemia causes an increase in extracellular osmolality, which then leads to elevated potassium levels. Hyperkalaemia will be prolonged if duration of heparin therapy is prolonged before discontinuation.
Conclusion
This case illustrates the potentially harmful effect of low dose low-molecular weight heparin. Although there are warnings in the British National Formulary about the risks of hyperkalaemia with heparin use, awareness of this side effect amongst medical and surgical staff appears to be low. With increasing use of prophylactic heparin amongst medical patients, heparin-associated hyperkalaemia may well be seen more frequently.

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P274

A rare variant of papillary carcinoma of thyroid: Warthin-like variant

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Introduction
Warthin-like papillary thyroid carcinoma (WLPTC) is a rare variant of thyroid papillary carsinoma (TPC). We present these cases to point out this rare variant.
Case reports
Case 1: A 38-year-old woman admitted to outpatient clinic with a thyroid nodule. Ultrasonography of thyroid gland revealed bilateral multinodular goiter with

microcalcifications. Thyroid autoantibodies were elevated. Thyroid function tests (TFT) were normal. Fine-needle aspiration (FNA) was suspicious for papillary carcinoma. She underwent total thyroidectomy and regional lymph node dissection. Histopathological diagnosis was bilateral, multifocal WLPTC. Microscopically, three tumor foci were detected on severe chronic lymphocytic thyroiditis (CLT) background. The largest tumor was 10 mm in right lobe. Lymphovascular invasion and extrathyroidal extension were absent. Post-operative stimulated thyroglobulin (Tg) levels were elevated (50.2 ng/ml). Suppressed Tg levels were under 0.2 ng/ml. Radioactive iodine treatment wasn't performed. The patient was followed with neck ultrasonography for a year and no metastases were detected.
Case 2: A 28-year-old woman admitted to outpatient clinic with a thyroid nodule. Thyroid ultrasonography showed a 12×8×6 mm nodule with microcalcification on right thyroid lobe. Thyroid autoantibodies were elevated. TFT were normal. FNA cytology of thyroid nodule was reported as suspicious for malignancy. Total thyroidectomy was performed. Histopathological diagnosis was locally invasive WLPTC underlying severe CLT in right lobe. Tumor diameter was 13 mm. There was local capsular invasion but not vascular invasion, lymph node metastasis or extrathyroidal extention. Stimulated Tg levels were under 0.2 ng/ml. Radioactive iodine treatment was not performed. She was followed with neck ultrasonography for a year and no metastasis was detected.
Conclusions
WLPTC is a variant of TPC with good prognosis. Low risk patients can be followed with reserving RAI treatment for only selected cases.

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P275

Mixed medullary and papillary carcinoma of thyroid

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Introduction
Despite having different embriogenic origins, thyroid medullary carcinoma and follicular carcinoma may be seen together as mixed medullary-follicular thyroid carcinoma. We present a rare case of mixed medullary-follicular cell carcinoma of thyroid which has a progressive and aggressive nature.
Case report
A 68-year-old female patient admitted with complaint of a lump in her neck. Ultrasonography of thyroid gland revealed a 37×35 mm solid mass. Fine-needle aspiration biopsy was reported as 'suspicious for papillary or follicular carcinoma'. Patient underwent total thyroidectomy and right selective neck dissection. Pathology report showed diffuse invasive follicular carcinoma. Tumor diameter was 5 cm and there was capsular and lymphovascular invasion. Patient received radioactive iodine (RAI) treatment. Posttreatment whole body imaging (WBI) revealed only postoperative residual thyroid tissue. Owing to discrepancy between increased thyroglobulin levels and negative WBI results, positron emission computerized tomography scan was obtained. Metastasis was noted between left lower pulmonary lobe and second lumbar vertebral body (L2) Vertebral metastasis was confirmed with magnetic resonance imaging The patient received radiotherapy to L2. However, she had a rapidly growing right cervical mass within 3 months. Neck CT comfirmed a 54×38×29 mm lymph node package. Owing to agressive nature and lack of improvement upon RAI treatment as suggested by lack of iodine uptake by metastatic lesions in WBI, pathologic specimens were re-evaluated. It was reported to be mixed medullary–follicular carcinoma. Tumor cells has been stained positively with carcinoembryogenic antigen, synaptophysin, chromogranin and calcitonin Excisional biopsy result of neck mass was reported as carcinoma infiltration. The patient received radiotherapy to neck mass and is still followed-up under thyroid stimulating hormone suppression.
Conclusions
In the presence of differentiated thyroid carcinomas resistant to RAI treatment and agressive and progressive nature, possibility of a mixed form carcinoma should also be considered.

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P276

Morphological and functional imaging allow better characterization of brown tumors in a patient with severe primary hyperparathyroidism

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Introduction
Brown tumors are rare, destructive, osteolytic bone lesions, occurring in advanced stages of hyperparathyroidism, due to increased osteoclastic activity.
Case report
A 25-year-old woman presented with recent, intractable pain on the right shoulder and with hypercalcemia (Ca, 3.93 mmol/l) related to severe primary hyperparathyroidism (PTH, 494 pg/ml). Multiple osteolytic lesions, detected on the upper extremity of the right humerus, distal right radius, sternal end of the right clavicle, right acromion and bilateral sacroiliac joints were depicted having intense uptake on Tc-99m tetrafosmin scan. Tc-99m-HDP whole body bone scan coupled with low dose CT, realized 24 h later, revealed decreased uptake in the humeral head tumor, associated with large areas of osteolysis lined by thinned and expanded cortical borders, while all other osteolytic bone lesions still presented increased uptake. Both CT and MRI identified the localization of these benign tumors, while the pathology assessment of the humerus tumor confirmed the diagnosis. Left superior parathyroid adenoma was detected by parathyroid scintigraphy and surgically removed, with consequent improvement in bone pain and calcification of the lytic lesions. However, the large humeral brown tumor was still responsible for functional impotence two months after parathyroidectomy, thus necessitating orthopedic assessment for arthroplasty.
Conclusion
Large brown tumors exhibiting intense Tc-99m-tetrafosmin uptake while lacking Tc-99m-HDP uptake are active tumors with an important lytic component, necessitating complex investigations and follow-up. Our case emphasizes the necessity of a multimodality imagistic approach to optimize the assessment of the severity and the extent of brown tumors, allowing multidisciplinary specific therapeutic options.

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P277

When mother and daughter become father and son

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Gender dysphoria (GD) leading to hormonal treatment and sex reassignment surgery that spans two generations has not been reported so far.
The mother was diagnosed with GD at the age of 47. As an only child she suffered from emotional, physical, and sexual abuse by her parents. From the age of 3, she fantasized being a boy and started behaving like one. During later youth the genderdysphoric feelings were repressed. She married at the age of 18. One year later she became pregnant, but after giving birth she felt no emotional connection with the baby-girl. A diagnosis of GD was established in 2004. The client started with cross-sex hormone therapy. In 2006 he underwent bilateral subcutaneous mastectomy and endoscopic hysterectomy/ovariectomy. Metadoioplasty followed by phalloplasty were performed in 2007 and 2009 respectively. In 2012, the sex reassignment surgery was completed with the placement of an erectile device and testicular prostheses.
The daughter was diagnosed with GD at age 31. She was also an only child. She has no traumatic childhood memories. GD became obvious from the age of 8, when she started behaving like a boy and sought for male playmates. During later youth she suffered from psychological problems such as panic attacks and social phobia.
A diagnosis of GD was established in 2007. In 2008, cross-sex hormone therapy was started. Bilateral subcutaneous mastectomy and endoscopic hysterectomy/ovariectomy were performed in 2009. Because of a postoperative complication after the mastectomy genital surgery is temporarily postponed.
Both father and son are doing well since their transition. Genetic testing showed an aberrant female array CGH profile with a ~650 kb duplication in chromosome

15q26.3 both in father and son and a ~100 kb deletion in 7p14.1 in the *GLI3* gene in father. Further research into the clinical relevance of this finding or its connection with GD is currently ongoing.

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P278

Giant mediastinal parathyroid cyst with hyperparathyroidism: a case report

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Primary hyperparathyroidism (PHPT) is rarely caused by parathyroid adenoma with cystic degeneration, especially by the cyst localized in mediastinum. Both differential diagnosis of mediastinal cyst and management of the patient can be challenging.

Case presentation

A 57 years old woman was transferred from district hospital where her urosepsis and nephrolithiasis had been treated successfully. A liquid collection in left hemithorax had also been found during radiological examination. She underwent thoracocentesis under CT because empyema had been suspected as a source of sepsis. Neither pus nor malignancy was found at cytological examination. Her serum parathormon (PTH) was high–14, later 78 pmol/l (normal range 1–7) together with serum calcium 2.62 mmol/l (2.15–2.55), ionized calcium 1.99 mmol/l (0.9–1.3), phosphate 0.61 mmol/l (0.84–1.45), and albumin 25.9 g/l (34–48). The situation suddenly became complicated with pancreatitis, symptoms from compression by large cyst and recurrent fever. Her calcium levels were only transiently stabilized after treatment with Cinacalcet (Mimpara) and calcitonin. We also performed neck ultrasound, neck MRi and 99mTc_MIBI scintigraphy with negative results. We performed again punction of the cyst, but the PTH level in the cyst fluid was lower (4173 pg/ml) than in serum (6915 pg/ml, normal range 13–50). When our patient became stable, without fever after antibiotic treatment, we performed left lateral thoracotomy with extirpation of the cyst. Parathyroid adenoma with cystic degeneration with residual atrophic thymic tissue was confirmed by histological examination. The serum calcium and also PTH are normalized after the surgery without any treatment and our patient is doing well.

Conclusion

We are presenting rare case of primary hyperparathyroidism caused by parathyroid adenoma with cystic degeneration, localized in mediastinum. Diagnostic of cyst in this localization can cause pitfalls.

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P279

Three endocrine neoplasms: an unusual combination of pituitary adenoma, papillary thyroid carcinoma, and follicular thyroid carcinoma

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Background

Differentiated thyroid cancer is the most frequent thyroid tumor. Combinations of follicular carcinoma and papillary carcinoma are seen. Functional pituitary adenoma coexisting with differentiated thyroid carcinoma was reported previously in literature. We report a 47-year-old women with three different synchronous endocrine tumors; papillary thyroid cancer, follicular thyroid cancer, and prolactinoma.

Case

A 47-years-old female patient was admitted to out-patient clinic with oligomenorrhea and galactorrhea. Except patient's prolactin (PRL) raise, hormonal levels were in normal ranges (PRL: 186 ng/ml). Macroprolactin was negative. Pituitary MRI demonstrated a mass 9×11 mm. Cabergolin 0.5 mg/twice a week was started. She was euthyroid and thyroid autoantibodies were in normal ranges. In thyroid US, 17×10 mm nodule in left lobule, 21×19 mm nodule in right lobule, and 8×7 mm nodule in isthmus were detected. Fine needle aspiration biopsy suggested suspicious for follicular neoplasm for nodule in right lobule, benign for left one. She underwent total thyroidectomy. The histopathological examination revealed presence of a follicular cancer within right lobule (2 cm) and multifocal papillary cancer (0.5, 0.8, and 1.2 cm) within left lobule. Radioactive iodine was given to patient after surgery.

Conclusion

Underlying pathological cause of most pituitary adenomas remains unclear despite the recent identification of a number of potential molecular genetic abnormalities. Pituitary tumor transforming gene (PTTG) initially isolated from pituitary tumor cells. PTTG protein is expressed at higher than normal levels in several tumors, including those of the pituitary, thyroid, colon, ovary, testis, breast, and hematopoietic neoplasms. Co-existence of three endocrine tumors in our case may be caused from different causes. It may be releated with the potential molecular genetic abnormalities like PTTG. Or, incidental occurrence of them may be a reason, because each tumor occurs with a high prevalence in population.

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P280

Not a make-up, but an alarm signal of a new onset of Addison's disease

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Case report

A 52-year-old woman had an appointment at the dermatology department for a previous diagnosis of melasma. She was seen in October and her pigmentation had appeared somewhere during summer. She did not recall any drug intake, she denied sun exposure in the recent past, and she was a social employee working indoor.

At the clinical examination intense hyperpigmentation around the eyes was noted. In contrast with the rest of the skin of normal aspect. The pigmentation was very well demarcated with no symptoms associated.

Our first gesture was to ask the lady to use a cotton swab to clear the make-up, obviously with no results. Local trauma and melasma were excluded from the beginning.

A minutious clinical examination was performed, but remained unremarkable; no history of fatigue or anxiety, no sleep disturbance, no loose of appetite or weight loss, no complaints. Blood pressure and pulse were normal.

Routine laboratory investigations were within normal range including fasting blood, serum urea, creatinine and electrolyte; anti-HIV, anti hepatitis C virus hepatitis B surface antigen (HCV and HBsAg) factors were negative.

Owing to a suspicion of Addison's disease an early morning cortisol level was asked and turned to be below normal value. A diagnosis of Addison's disease was supported and the patient was sent to the endocrinology department for further investigations and close monitoring of the disease.

As dermatologists is important to be able to recognize and suspect Addison's disease in front typical skin lesions: cutaneous and mucosal hyperpigmentations, thin and brittle nail, and scanty body hair. Pigmentation can be homogenous or mottled, may be present on the skin, but also oral cavity, conjunctiva, and genitalia. Specific pigmentation of gingival, vermillion border of the lips, buccal mucosa, palate, and tongue may raise the suspicion of Addison's disease even in the absence of other clinical signs.

The present case stresses the importance of an early diagnosis of Addison's disease in the context of a peculiar hyperpigmentation in the absence of other signs and symptoms.

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P281

A carotid body tumor mimicking a thyroid nodule: a case report

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Introduction
The cases of paragangliomas (PGLs) mimicking thyroid nodules were also reported in literature rarely. We will present a case of PGL (a carotid body tumor) that we initially evaluated as a thyroid nodule, and then diagnosed as a PGL.
Case report
A 74-year-old woman was admitted due to a mass in the right side of neck growing rapidly within the last 1 month. Physical examination revealed a hard and painless mass with smooth surface, extending from right thyroid lobe level to angulus mandibula. THS, free triiodothyronine, and free tetraiodothyronine were within normal ranges. Multinodular goitre was detected on ultrasound (US). US-guided fine-needle aspiration biopsy was performed in 3 nodules, and the nodules were reported to be benign. Core needle biopsy was performed for the nodules in right thyroid lobe due to suspected thyroid malignancy, and histopathological findings were found to be consistent with neuroendocrine tumor. Bilateral total thyroidectomy were performed, and during the surgery, a mass of 4×3 cm was seen in the right carotid artery bifurcation and excised. Microscopically, the tumor cells were arranged in well-defined nests (Zellballen) and encircled by a thin layer of S-100 protein and GFAP positive, and spindle-shaped sustentacular cells. Tumor cells vary in size and shape, and have a finely granular cytoplasm. The nuclei were round to oval with coarsely granular chromatin with a so-called salt- and-pepper appearance. In tumor cells, immunohistochemical CD56, synaptophisin, neuron specific enolase and chromogranin A were positive, but calcitonin, TTF-1 and Tg were negative. In light of these findings, the case was diagnosed with PGL, and the histopathologic findings of other thyroid nodules were consistent with colloidal nodules.
Conclusion
Cervical PGLs are uncommon tumors, so healthcare providers should take the likelihood of PGLs into account in the differential diagnosis of neck masses.

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P282

An uncommon infiltrative disease of thyroid: Riedel's thyroiditis

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Introduction
Riedel's thyroiditis, also known as invasive fibrous thyroiditis, is a rare disorder of unknown etiology in which characterized by invasive fibrosis that partially destroys the thyroid gland and extends into adjacent neck structures. The diagnosis of Riedel's thyroiditis is clinically difficult because this form of thyroiditis can mimic lymphoma or Hashimoto's thyroiditis during preoperative radiologic, and pathologic examination. Sonographic features resemble thyroiditis with adjacent soft tissue extension.
Case report
A 60-year-old woman admitted to our institution with neck swelling without pain, dysphagia, dyspnea, and a recent history of hoarseness. On physical examination, there was a diffuse firm painless swelling in the anterior neck. Her serum free thyroxine, free triiodothyronine, and TSH levels are 1.40 ng/dl, 2.52 pg/ml, and 1.88 μIU/ml, thyroglobulin of 0.1 ng/ml (1.6–59.9 ng/ml), anti-thyroglobulin Ab of >1000 IU/ml (0–4.11 IU/ml), and anti-thyroid peroxidase Ab 405.7 IU/ml (0–5.61 IU/ml). Ultrasonography, computed tomography, and magnetic resonance imaging (MRI) of the neck revealed. All showed a diffusely enlarged mass covering both thyroid lobes, extending to the infra-hyoid level and encircling thyroid cartilage. This mass caused tracheal stenosis, but there was no evidence of tracheal invasion on MRI. Fine needle aspiration cytology revealed suspicious for lymphoma. Open-neck surgery was performed. surgical resection of the thyroid gland was successful but resection of soft tissue invasion was unsuccessful because the soft tissue invasion was markedly fibrotic. The final pathological diagnosis was Riedel's thyroiditis. Histologically, the tumor showed extensive replacement of the thyroid parenchyma with dense keloidal fibrosis, intermixed well-developed lymphoid follicles, scattered lymphocytes, and plasma cells. After surgery l-thyroxine replacement therapy was started.
Conclusion
Ultrasonografic features of Riedel's thyroiditis similar to malign thyroid lesions and frequently misdiagnosed as lymphoma on fine-needle aspiration cytology. Diagnostic thyroidectomy should be performed for the accurate diagnosis and treatment for Riedel's thyroiditis.

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P283

Primary hyperparathyroidism due to parathyroid carcinoma: case report

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Introduction
About 1% of primary hyperparathyroidism is due to parathyroid carcinoma. The affected gland is often indistinguishable from atypical adenoma. The proper diagnosis is usually made when the disease recurs or metastases are present and then is connected with poor prognosis.
Case report
A 49-year-old man, after resection of parathyroid adenoma (postoperatively with normalization PTH concentrations and hungry bone syndrome), with limbs' fractures due to fall from his height, was admitted to Department of Endocrinology because of high serum levels of PTH (913 pg/ml; *n*,14–72) and calcium (13.0 mg/ml; *n*,8.4-10.4). MIBI and CT scans showed enlarged lower right parathyroid gland. Reoperation and total strumectomy of the right lobe was performed but the decrease in PTH and calcium levels have not been observed. Few weeks later, Ca and PTH increased to 17.7 mg/dl and 2910 pg/ml respectively. Additionally left kidney nephrolithiasis, brown tumours of the iliums and in the skull have been observed. 18-FDG PET–CT showed metabolic active lesion on the left side of the trachea which has been removed. Histological postoperative examination confirmed the suspected diagnosis of parathyroid carcinoma. After short-term improvement, PTH and calcium concentrations increased again (PTH, 5570 pg/ml; Ca, 16.8 mg/dl). The check-up CT revealed reccurent peritracheal patological mass (19×25×30 mm) with the impression of the oesophagus. After fourth non-radical surgery, decrease but not normalization in PTH and Ca levels have been achieved. The patient was disqualified from radio- and chemotherapy. To manage hypercalcaemia, besides typical treatement, zoledronic acid, pamidronian, and cinacalcet have been used. Unfortunately, renal impairment, swallowing disturbances, and dyspnea have been appeared. Twelve months later after the diagnosis of primary hyperparathyroidism the patient died beacause of respiratory and cardiac failure.
Conclusions
Rare prevalence of parathyroid cancer, lack of typical symptoms and histological features usually cause delay in diagnosis that deteriorates prognosis. Therefore parathyroid carcinoma still remains diagnostic and management challenge for many physicians.

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P284

A rare cause of hypocalemia: familial hypoparathyroidism

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Background and aim
HDR syndrome, is a rare disease characterized with hypoparathyroidism, sensorineural deafness, and renal disease. Patients usually present with hypocalcaemia, tetany, or afebrile convulsions. Hearing loss is usually bilateral. Renal disease includes renal dysplasia, hypoplasia or aplasia. We report a Turkish family of HDR syndrome.

Cases
A 56-year-old hypocalcemic deaf male patient and his daughter (25 years) and son (21 years) with hypocalcemia and sensorineural deafness. Chvostek's and Trousseau's tests were positive and bilateral sensorineural deafness was determined in all three patients. Other physicial examination findings were normal in physical examination.
Laboratory
Routine examination of blood, urine, chest radiography, and hepatic function tests were normal. Serum calcium (6.8, 6.9, and 7.1 mg/dl), phosphorous (4.8, 4.8, and 5.2 mg/dl), 25-OH vitamin D (18.1, 16.7, and 14.4 ng/ml), PTH (11, 14, and 9 pg/ml) and 24 h urinary calcium excretion (36, 42, and 52 mg/24 h) were low respectively. A renal parenchimal atrophy in left kidney was determined in index case (father) by abdominal ultrasonographic examination. Computed tomography (CT) scan of brain showed bilateral cerebellar, basal ganglionic, and subcortical calcification in index case but electroencephalogram revealed normal background alpha activity in all cases.
Results
With the combination of hypoparathyroidism, sensorineural deafness and unilateral renal dysplasia (in father); patients were accepted as familial hypoparathyroidism. Unfortunately we could not performed genetic analysis due to technical failure.
Discussion
HDR or Barakat syndrome is a rare disease. Haploinsufficiency (deletions) of zinc-finger transcription factor GATA3 or mutations in the *GATA3* gene appear to be the underlying cause of this syndrome. The syndrome should be considered in infants who have been diagnosed prenatally with a chromosome 10p defect. Management consists of treating the clinical abnormalities at the time of presentation. Prognosis depends on the severity of the kidney disease. We report a Turkish family with HDR syndrome.

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P285

The coexistence of anaplastic thyroid carcinoma and papillary thyroid carcinoma: two case reports

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Introduction
Anaplastic thyroid carcinomas (ATCs) are sometimes accompanied by well-differentiated carcinomas (WDCs), and ATCs have been speculated to be dedifferentiated from the preexisting or coexisting WDCs. We will present two cases determined with both ATC and papillary thyroid carcinoma (PTC.)
Case 1
A 82-year-old woman was investigated due to a painful neck mass. Thyroid function tests were normal. Thyroid ultrasonography revealed isohypoechoic nodules in sizes of 45 and 13.5 mm in right lobe and an isoechoic nodule in size of 11.3 mm in left lobe. Fine-needle aspiration biopsy (FNAB) was performed, and PTC was detected in both nodules on the right. Bilateral total thyroidectomy was performed, and in pathological investigation, the nodule of 45 mm in the right lobe was seen to be an ATC including regions of classical variant PTC. Additionally, the pathology of the nodule of 13.5 mm in the right lobe was consistent with classical variant PTC. PET/CT revealed the involvements of increased 18-FDG consistent with metastasis, and due to the metastatic condition in the case, radiotherapy was performed.
Case 2
A 62-year-old male presented to our clinic complaining of a neck lump and dysphagia. Physical examination revealed 4 cm mass and cervical lymph nodes on the left side of the neck. Thyroid function tests were normal and thyroid ultrasonography revealed hypoechoic nodule in sizes of 41 mm in the left lobe. Two FNABs were reported as nondiagnostic. Bilateral total thyroidectomy and left lymph node dissection were performed. The postoperative pathology report was a 3 cm ATC in the left lobe and a 5 mm PTC in the right lobe. He was given radiotherapy.
Conclusion
PTC followed by poorly differentiated and follicular carcinoma are most frequently cited to coexist or as precursors of ATC. The early diagnosis of thyroid carcinoma results in a decrease of the incidence of ATC.

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P286

One month-Tadalafil 5 mg once daily administration improves clinical and ultrasound parameters of chronic pelvic pain syndrome/lower urinary tract symptoms

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Introduction
Tadalafil 5 mg once daily (T5od) has been recently approved by the Food and Drug Administration for the treatment of lower urinary tract symptoms (LUTS), along with erectile dysfunction (ED). Recent pooled data analyses demonstrated that T5od–International Prostate Symptom Score related improvements were significant regardless of confounders. In addition, PDE5 inhibitors exert a positive effect on ejaculatory latency. We assessed the clinical outcome of 30 days-T5od administration on a patient complaining of CPPS/LUTS.
Case report
A Caucasian men of 27 years presented for chronic pelvic pain syndrome (CPPS) and LUTS. He has been complaining since one month of CPPS, LUTS, mild ED and acquired premature ejaculation. He underwent, before and after treatment, medical history assessment, complete physical examination, scrotal and transrectal color-Doppler ultrasound (CDUS) before and after ejaculation, semen analysis including seminal interleukin 8 (sIL8) measurement, and validated questionnaires exploring CPPS (National Institutes of Health–Chronic Prostatitis Symptom Index (NIH–CPSI)), LUTS (International Prostate Symptom Score (IPSS)), sexual and erectile function (International Index of Sexual Function-15, (IIEF-15) and (IIEF-15–erectile function domain (EFD) respectively), ejaculatory status (Premature Ejaculation Diagnostic Tool PEDT) and psychological symptoms (Middlesex Hospital Questionnaire). After treatment the patient showed an improvement in NIH-CPSI (22→17) and IPSS (23→14) scores. Global sexual and erectile functions, assessed by IIEF-15 (58→68) and IIEF-15-EFD (24→27) respectively, improved, as well as ejaculatory latency (PEDT score 14→11). Psychological status, assessed by MHQ, showed a consistent amelioration (19→7) at the end of the treatment. We also observed an improvement in biochemical and CDUS parameters related to prostate-vesicular inflammation. In particular, a reduction in sIL8 levels (8.15→6.14 ng/ml) and a significant improvement in arterial peak systolic velocity (12.7→6.8 cm/s), parameters related to prostate inflammation and CPPS, were observed after treatment.
Conclusion
A 30 days-T5od administration seems to exert an improvement in CPPS/LUTS, biochemical and CDUS parameters of prostate inflammation, along with psycho-sexual function.

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P287

Recurrent episodes of hypoglycemia caused by insulinoma in a patient with type 2 diabetes mellitus

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Introduction
Hypoglycemia is the most frequent metabolic complication observed in patients with type 2 diabetes mellitus (T2DM). Moreover, rare insulinomas are the most common cause of endogenous hyperinsulinemic hypoglycemia in adults. The coincidence of insulinoma in a patient with pre-existing T2DM is an extremely rare condition and there are few case reports in the medical literature.
Case report
A 76-year-old woman diagnosed with T2DM 6 years ago, was referred to our hospital because of recurrent episodes of hypoglycemia. Her diabetes was treated with metformin, 1750 mg/day having a good metabolic control (HbA1c: 5.7%). About 4 years after she was diagnosed with T2DM, she had experienced an initial episode of hypoglycemia. The dose of oral anti-diabetics was reduced. However, although drug dose was lowered hypoglycemic events began to be recurrent. Even though the therapy was discontinued at the end, persistent episodes were still occurring. Complete physical examination was normal. Her laboratory profile showed normal renal and liver functions. Also, thyroid and adrenal dysfunctions were excluded. Laboratory profile from a prolonged fasting test showed inappropriately elevated plasma insulin and C-peptide levels in presence of hypoglycemia (plasma glucose, 36 mg/dl; insulin, 67.1 mU/ml; and C-peptide, 8.97 ng/ml). A CT-scan revealed a 2.2 cm sized mass in the pancreatic tail. The patient underwent surgery and hystopathological diagnosis revealed insulinoma.

One year after resection, C-peptide levels and plasma insulin are in normal range and hyperglycemia due to T2DM persists. She is currently being managed with gliclazide 90 mg/day without any further hypoglycemic events.
Conclusions
If hypoglycemia persists despite stopping diabetes treatment, other causes should be considered. Although this is an infrequent condition, clinicians should bear in mind that insulinomas may exist together with T2DM, and it is important to have this suspicion for the prevention of morbidities.

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P288

Primary hyperparathyroidism due to ectopic mediastinal parathyroid gland at the level of anterior wall of ascending aorta

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Introduction
Parathyroid adenoma is the most common cause of primary hyperparathyroidism (PHPT) resulting in hypercalcemia and hypercalciuria due to autonomous secretion of PTH. Ectopic parathyroid adenoma, as a consequence of variability in the glandular tissue migration during the embryologic life or a supernumary fifth parathyroid gland, has an incidence of 25% among patients with PHPT. The incidence of deeply mediastinal ectopic parathyroid adenoma is 1–3%.
Case report
We report the case of a 61-year-old woman who was discovered with hypercalcemia during routine check for postmenopausal osteoporosis. Calcium levels ranged between 10.8 and 12 mg/dl (8.5–10.2), with increased PTH levels 203 pg/ml (10–65), $P = 2.5$ mg/dl (2.4–4.9); Creat = 0.8 mg/dl (0.6–1.2); 25(OH) $D_3 = 23.2$ ng/ml (10–60); ALP = 204 U/l (<280); and Mg = 2.1 mg/dl (1.6–2.4). The 24 h urinary Ca was elevated 343 mg/24 h (100–300) and $P = 507$ mg/24 h (350–1300). DXA screening revealed osteoporosis in both lumbar spine and femoral neck. Primary hyperparathyroidism was diagnosed and further investigation for localization of the adenoma was carried out. Cervical sonography was unremarkable. Tc-99m-sestamibi scintigraphy was carried out and an accumulation area indicating ectopic parathyroid tissue in the anterior mediastinum, at the level of aortic arch, was demonstrated. Additionally chest-cervical CT scan revealed a 1.7 cm nodule in the anterior mediastinum at the level of anterior wall of ascending aorta. The patient underwent surgical resection of the ectopic parathyroid gland by median sternotomy. PTH and calcium serum levels normalized after surgery (41 pg/ml and 9.5 mg/dl respectively). No calcium and/or alfacalcidol supplements were needed postoperatively.
Conclusion
Ectopic parathyroid adenomas with mediastinum localization proximal to ascending aorta are rare causes of primary hyperparathyroidism. Those masses are considered to be derived from migrating inferior parathyroid glands to anterosuperior mediastinum. Combination of Tc-99m-sestamibi scintigraphy and chest-cervical CT scan are indispensable for the preoperative localization of oversecreting parathyroid tumors.

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P289

Rhabdomyolysis precipitated acute renal injury during levothyroxine withdrawal for remnant ablation in a case with papillary thyroid cancer

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Ever since the approval of recombinant human TSH (rhTSH) prior to remnant ablation and whole body scans, usage of levothyroxine withdrawal for TSH elevation is decreasing. However the readily unavailability of rhTSH in some countries and the cost are its disadvantages. Withdrawal of levothyroxine, however, exposes the subjects to hypothyroidism.
A 26-year-old male patient admitted to our hospital for a routine checkup with no symptoms. His TSH level was 7.54 mIU/l (0.35–4.2) thus a thyroid ultrasonography was performed. A $12 \times 10 \times 20$ mm thyroid nodule was visualized in the left lobe and the thyroid parenchyma was compatible with Hashimoto's thyroiditis. We performed a fine-needle aspiration biopsy from the nodule which was reported suspicious for papillary thyroid cancer. The same week he underwent total thyroidectomy confirming the diagnosis of classical type papillary thyroid cancer. The tumor was 17 mm in diameter with no extra capsular or extra thyroidal invasion. We planned 100 mCI of radioactive iodine (RAI) for remnant ablation 8 weeks after the surgery. We withdrew levothyroxine 4 weeks before the planned RAI and initiated T_3 replacement which was also withdrawn 2 weeks before the scheduled RAI treatment. Two days before the scheduled RAI, the patient complained of fatigue and nausea. His serum creatinine level was 2.1 mg/dl (0.6–1.1), K 4.2 mEq/l, and creatinine kinase level was 1300 μg/l (10–120). At this point his TSH level was 50 mIU/l (0.45–4.2) and free thyroxine level was 0.5 ng/l (0.9–1.48). He was hydrated orally and parentally. Levothyroxine was initiated after the RAI and the creatinine level decreased gradually to normal limits.
Symptomatic hypothyroidism is frequently observed during levothyroxine withdrawal prior to remnant ablation with RAI. Many case reports have been presented relating hypothyroidism to rhabdomyolysis. The presented cases were generally newly diagnosed subjects with probably long-standing hypothyroxinemia. Although rare, severe hypothyroxinemia caused by temporary withdrawal levothyroxine for RAI can precipitate rhabdomyolysis and acute renal damage. Since severe side effects can occur during levothyroxine withdrawal besides symptoms of hypothyroidism, rhTSH may be preferred for TSH elevation when available.

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P290

46,XX/47,XXY mosaic form of klinfelter syndrome with ambiguous genitalia: a case report

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Klinefelter's syndrome (KS) is the most frequent form of sex chromosome aneuploidy. The classic form of KS is associated with a 47,XXY karyotype. Mosaic forms of KS are thought to occur in approximately 10% mainly in the form of 46,XX/47,XXY. Other forms of mosaicism are rare among which the 46,XX/47,XXY form is very rare and can manifest as an ambiguous genitalia at birth as reported in our case.
A full term child presented at birth an hypospadias with a cured penis of 2.5 cm length, the scrotum was well developed with the two gonads present inside. There was no other physical abnormalities. Ultrasound imagining confirmed the presence of two gonads in the scrotum and didn't found internal female genitalia. The hormonal assessment performed at three months found normal gonadotropins levels (LH = 10.74 Mu/ml, FSH = 5.19 Mu/ml) and a normal testosterone response after HCG stimulation (before HCG = 2.87 nmol/l, after HCG = 16.12 nmol/l). The karyotype found a 46,XX/47,XXY mosaic.
Mosaic forms of KS may explain the wide clinical spectrum of this disease. The 46,XX/47,XXY form may account for the more severe form with ambiguous genitalia as reported in our case.

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P291

Primary hyperparathyroidism caused by mediastinum located ectopic parathyroid adenoma resected by video-assisted thoracic surgery

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Introduction
Ectopic parathyroid adenomas are detected 16% of patients operated for primary hyperparathyroidism and 22% of them may be located in the anterosuperior mediastinal region. Herein we present a rare case of primary hyperparathyroidism

with severe long-term elevated parathormone (PTH) levels due to ectopic parathyroid adenoma in mediastinal region that was successfully treated by using video-assisted thoracic surgery (VATS).
Case report
A 38-year-old female admitted to our clinic with long-term complaints of severe hip pain and gait disturbance. In laboratory tests, serum calcium (Ca): 11.64 mg/dl (8.5–10.5), alkaline phosphatase (ALP): 764 U/l (35–105), phosphorus: 1.51 mg/dl (2.5–4.5), PTH 1385 pg/ml (15–65). The bone mineral density showed osteoporosis. X-ray radiography demonstrated extensive osteoporosis in the vertebrae, humerus, and femur. Urinary USG showed cortical millimetric calcifications in interpolar part of left kidney. No adenoma or hyperplasia was seen on neck USG. Parathyroid SPECT demonstrated a 27×48 mm lesion starting from first costosternal joint on the left mediastinal midline surrounding the aortic arch and reaching to parasternal area. Thorax CT revealed a 46×20×31 mm hypodense lesion located anterior to aortic arch in anterior mediastinal fatty tissue. Parathyroid adenectomy was performed via left VATS by the Thoracic Surgery Department. Postoperative 1st day both Ca: 6.79 mg/dl and PTH: 150 pg/ml levels were decreased and phosphorus level was return to normal range. Hungry bone syndrome (HBS) occured 48 h after surgery. Calcium and phosphorus levels were improved in 10 days by supplementation calcium and alfacalcidiol.
Conclusion
This is a rare case due to severe osteoporosis by large ectopic parathyroid adenoma in the mediastinum in a premenopausal woman that success recovery achieved via VATS. The cosmetic results of VATS is superior to sternotomy or thoracotomy and morbidity rate is low.

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P292

Insulinoma and pregnancy: a case report

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Insulinoma is the most common cause of hypoglycemia related to endogenous hyperinsulinism in adults. It is very rare in pregnancy, fewer than 30 cases of insulinoma presenting in pregnancy have been reported so far and it's managment is very challenging. We raported here the case of a pregnant women aged 35 years presenting an insulinoma.
The diagnosis was made 1 year ago in the presence of hypoglycemia, high levels of inulin and C-peptide and a 10 mm tumor in the body of the pancreas detected with endoscopic ultrasound. The patient was operated on but the surgery failed and hypoglycemia recurred few months later with the same biological and radiological findings as preoperatively. While the patient was waiting for reoperation a pregnancy occured with worsening of the hypoglycemic episodes in the first trimester as reported due to the increase in insulin sensitivity during early pregnancy, the patient was successfully managed with frequent feedings hoping that hypoglycemia will improve during the second and third trimester with the rise of isulin resistance, thereafter the patient will be operated after delivery.

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P293

Excessive stimulation of TSH receptor during pregnancy

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We are presenting a female, aged 34, who underwent two pregnancy miscarriages, in the 7th and 8th weeks. The first studies of thyroid hormones were made during the second pregnancy, and pointed to hyperthyroidism.
After the loss of her second pregnancy, she was diagnosed for thyroid disease and miscarriages. TSH, FT_3, FT_4, antibodies TPO, TG, and TRAB were normal. Ultrasound examination showed symmetrical thyroid, not enlarged, with the presence of heterogeneous small areas in both lobes. Fine-needle biopsy showed benign lesions. In thyroid scintigraphy with the radioisotope technetium there was no evident autonomy.
After half a year, patient reported in the 7th week of third pregnancy with the symptoms of hyperthyroidism. Clinically she presented tachycardia, did not gain weight and vommitted.
Laboratory it was noticed greatly increased thyroid hormones with extremely high hCG: 197 877 mIU/ml concentration in the blood serum. Gynecological ultrasonography showed living fetus corresponding to the 7th week of pregnancy. Chorion showed no signs of detachment. Patient was treated with Propylthiouracil, progesteronum, folic acid and i.v. hydratation.
In the 12th week occurred normalization of hormone levels, a decrease of hCG, antithyroid drug was discontinued. She remains under the care of a gynecologist, endocrinologist, pregnancy is developing normally.
Conclusions
Often at the beginning of the pregnancy occurs hyperthyroidism caused by TSH-like properties of hCG. It was calculated that hCG is ~1/4000 thyrotropic activity of human TSH. The physiological effects of hCG causes hyperthyroidism, but does not lead to pregnancy loss.
In this case, there has been a miscarriage of two successive pregnancies. Therefore we conclude, that a very high concentration of hCG leading to severe thyrotoxicosis may be a causative factor of the pregnancy miscarriages.
In such a situation hypersensitivity to the TSH receptor hCG can not be excluded.

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P294

Brown tumors: the first and the final manifestation of primary hyperparathyroidism.

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Introduction
Brown tumor–well circumscribed lytic lesion is one of the complication of advanced stage of primary and secondary hyperparathyroidism. It may be also a first clinical sign of primary hyperparathyroidism. Nowadays this is rare manifestation in developed countries due to increased use of routine screening laboratory examinations. Brown tumors may also mimic true neoplasm and lead to misdiagnosis if close attention is not paid. We present three case reports and imaging documentation of patients admitted to our hospital with brown tumors – in two cases as first and in one case as a final manifestation of primary hyperparathyroidism.
Case report
We present a case report of 30-year-old pregnant woman (admitted at 31 week of first pregnancy) without medical past history with pelvic localization of brown tumor and a case of 54-year-old woman without medical past history with the brown tumor localized in left tibia. We finally present a case report of 36-year-old patient with long history of treatment of advanced osteoporosis, with nephrocalcinosis, after vertebroplasty of 7th and 12th thoracic vertebrae and after acute pancreatitis episode and pathological fracture of left humerus. The primary hyperparathyroidism was finally diagnosed after brown tumors localized in right foot were found.
Conclusions
i) Despite the rare occurrence of brown tumors it still can be the first manifestation of primary hyperparathyroidism.
ii) Despite many publications there is constant need of reminding about radiological and clinical manifestations of primary hyperparathyroidism, not only in endocrinological but also other specialities (orthopedical, radiological, etc.) journals. It may facilitate prompt diagnosis of this destructive disease.

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P295

Oncocytic carsinoma with sternum metastasis

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Introduction
Oncocytic (Hurthle cell) carcinoma is consisted of <5% of thyroid cancer but most metastasizing cancer type among differentiated thyroid cancer. We presented an oncocytic carcinoma with sternum metastasis.

Case
A 68-year-old women admitted to endocrinology policlinic with complaint of a mass in her neck. She was diagnosed hyperthyroidism and she was using thionamid for 6 months. Her medical history revealed hypertension for 3 years and asthma. In physical examination she had stage 3 guatr and fixed hard solid mass over sternum. In laboratory TSH and free T_4 was 0.06 μIU/ml (0.4–4.2 μIU/ml) and 07 ng/dl (0.8–2.7 ng/dl) respectively. In thyroid ultrasound in right thyroid lob the biggest nodule was 10 cm and in left lobe biggest nodule was 2 cm and thyroid gland was extending under sternum. Thyroid scintigraphy revealed hyperplastic thyroid gland with increased uptake and hypoactive nodules. In thorax CT there was a 5×5.5 cm mass on sternum that destructs the bone and invases to fat tissue of mediastinum. Thyroid fine-needle aspiration biopsy result was follicular neoplazm and biopsy of mass on sternum included atypical cells. Thyroglobulin washout was performed from mass on sternum and thyroglobulin level was >300 ng/ml. Bilateral total thyroidectomy and mass excision with partial sternum excision were performed by general surgery and thoracic surgery physicians. Postoperative thyroid pathology revealed well differentiated oncocytic carcinoma and pathologic result of sternum mass was metastasis of oncocytic carcinoma. Furthermore mediastinal and central lymph node metastasis detected. Radioiodine ablation performed to patients.
Discussion
Oncocytic cell carcinoma is considered a variant of follicular carcinoma. Metastasis is observed 34% of oncocytic carcinoma. Various studies reported that 'oncocytic carcinoma' is the most frequent cancer that metastasizes to bone. Even though oncocytic carcinoma has low radioactive iodin (RAI) uptake compared with follicular carcinoma, treatment of oncocytic carcinoma includes RAI ablation, so RAI ablation was performed to the patient. In light of this case we suggest scanning bone metastasis at the time of diagnosis among oncocytic carcinoma patients.

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P296

Type 2 polyglandular autoimmune syndrome and Turner syndrome

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Introduction
Individuals with Turner syndrome (TS) are prone to develop autoimmune conditions. The most frequently found are Hashimoto's thyroiditis, type 1 diabetes, coeliac disease, and inflammatory bowel disease. In patients with TS, Addison's disease isolated or combined with other autoimmune disease as type 2 polyglandular autoimmune syndrome, is a rare finding.
Case report
We report a case of a 41-year-old female patient, with severe asthenia, anorexia, and several episodes of lipothymia. Personal history of TS with a 45,X/46,XX karyotype, diagnosed when investigating for premature ovarian failure, vitiligo, and Graves' disease treated with 12 mCI of radioactive iodine with subsequent hypothyroidism. Physical exam showed marked melanodermia, BP=95/44 mmHg. Biochemical investigation: ACTH=2288 pg/ml (9–52), cortisol=3.6 μg/dl (5–25), active renin=124 μg/ml (7–76), aldosterone =9.9 pg/ml (40–310), DHEA, SO_4 <0.26 μg/ml (0.35–4.3), androstenedione <0.3 ng/ml (0.5–3.4), anti-21 hydroxylase antibody=8.9 U/ml (<1), K^+= 4.7 mEq/l (3.5–5), remaining laboratory results unremarkable. Rapid tetracosactide test: cortisol at 0'=4.5 μg/dl, at 60'=3.5 μg/dl. Type 2 polyglandular autoimmune syndrome screening: positivity of anti-GAD65 antibody (1.1 U/ml; $n<1$) and anti-insulin antibody (0.5 U/ml; $n<0.4$), but with no diagnosis criteria for type 1 diabetes; antiparietal cells antibody positive with elevated gastrin (1411 pg/ml; $n<90$) but with no pernicious anemia; coeliac disease and antiphospholipid antibodies were all negative. Abdominal CT revealed 'right adrenal gland almost unnoticeable, probably due to hypoplasia; left adrenal gland asymmetric, with decreased thickening of the left arm'.
The patient was started on substitutive therapy with hydrocortisone, 100 mg, t.p.d., i.v. and SOS until six times per day, then oral hydrocortisone 20 mg, s.i.d. plus 10 mg, b.i.d., fludrocotisone, 0.1 mg, s.i.d., thyroxine was decreased from 125 to 75 μg/day, with clinical and laboratorial improvement, having restarted her professional activity.
Conclusion
Patients with TS are at excess risk of autoimmune diseases, stressing the importance of a systematic screening during the follow up. In the event of one autoimmune endocrinopathy, most likely thyroid disease or type 1 diabetes, autoimmune polyglandular syndrome must be considered, as a timely diagnosis can reduce the morbidity and mortality potentially related with adrenal insufficiency.

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P297

Thyroid squamous cell carcinoma

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Introduction
Squamous cell carcinoma (SCC) is a very rare thyroid carcinoma with aggressive behavior and poor prognosis. Diagnostic difficulties reside in differentiating SCC from other thyroid malignancies and also in establishing its primary or secondary nature, which are both important for treatment strategy.
Case report
A 62-year-old woman, with unremarkable personal and family history, presented in October 2013 with progressive enlargement of a right neck mass with regional pain radiating toward the right ear and shoulder, hoarseness, inspiratory stridor and 10 kg weight loss in the past 2 months. Physical examination revealed a 5 cm hard, adherent thyroid nodule with impalpable inferior pole, without satellite lymph nodes. Laryngoscopy showed right vocal cord paralysis. On ultrasound the nodule was hypoechoic, with ill-defined margins, microcalcifications and necrotic areas. Contrast enhanced CT scan showed lateral impingement of neck vessels and trachea, retrosternal descent and intimate contact with the right brachiocephalic trunk. Lymph nodes or other masses were not identified (putative sites of origin or metastases). Thyroid hormones, antithyroid antibodies and calcitonin were normal, while thyroglobulin was low 1.43 ng/ml (NV 3.5–7.7). FNA cytology was inconclusive. Thyroidectomy was performed and histological examination revealed an infiltrative, malignant epithelial proliferation with keratinous foci, desmoplastic stroma, necrosis, hyalinization, and calcifications. Immunohistochemistry diagnosed SCC – focal positivity for p63, diffuse positivity for CK7, CK19, 34β E12, galectin 3 and negativity for TTF1 and CD5. The patient received three courses of Paclitaxel – 300 mg. In January 2014 thyroid recurrence was detected (three nodules up to 20 mm).
Conclusion
Future research is needed to establish a better management of patients with thyroid SCC.

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P298

Patient with alopecia areata

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Introduction
Alopecia areata affects 0.1–0.2% of population. It's pathogenesis has not yet been discovered, but genetic, autoimmune, vascular, psychogenic or neurological factors are being considered. It can occur in any age, but appears most commonly in late childhood, teenage or early adulthood. Alopecia areata commonly coexists with other diseases such as asthma, allergic rhinitis, atopic dermatitis, thyroid diseases and autoimmune diseases such as thyroiditis and vitiligo.
Case report
A 14-year-old patient was admitted to hospital presenting with overweight and alopecia areata lasting for 3 years. In the past medical history at the beginnig of

sympthoms also joints pain was present. Joints pain, increased CRP level and fever supported the diagnosis of reumatic fever, consequently the patient was treated with clarithromycin with a good clinical outcome, however in the last 6 months the patient has noticed elbow and shoulder joints pain again. On admission physical examination was remarkable for everweight, alopecia areata multilocularis of the scalp and enlarged thyroid gland. Laboratory findings demonstrated autoimmune thyroiditis with thyroid function tests within the normal range, increased level of anti-transglutaminase antibodies as well as Hep2 antinuclear antibodies. Basing on positive HLA–DQ2/HLA–DQ4 coeliac disease was diagnosed. Gluten-free diet was introduced.
Conclusions
The case illustrates significance of testing patients with alopecia areata for autoimmune diseases. Alopecia areata is one of the features present in patients with autoimmune polyendocrine syndrome type 1 (APS1).

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P299

Breast cancer in multiple endocrine neoplasia type 1

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Multiple endocrine neoplasia type 1 (MEN1) syndrome is an autosomal dominant familial tumor syndrome characterised by varying combinations of endocrine and non-endocrine tumors. Breast cancer is the most frequently diagnosed cancer in women, but presence of breast cancer in MEN1 is extremely rare.
A 36-year-old patient has been diagnosed with primary hyperparathyroidism, breast cancer and hyperprolactinemia due to a pituitary macroprolactinoma. Treatment with cabergoline was started and partial tumor regression was observed. In September 2012, partial parathyroidectomy, left breast quadrantectomy with axillary dissection and lipoma removal were preformed. Pathohistology finding revealed parathyroid adenoma and invasive ductal lobular breast cancer (GII, NII, ER7 (35%), PR (60%), HER2 1+, Ki67-10%). She continuated treatment with radiotherapy, chemotherapy (anthracyclines and docetaxel) and antagonist of the estrogen receptor (tamoxiphen) and so far she is in remission.
Abdominal MSCT scan showed micronodular adrenal hyperplasia which has proven to be biochemically nonfunctioning. Endoscopic pancreatic ultrasound and tumor markers were normal. Patient's father died at 65 due to pancreatic cancer. Owing to high suspicion to MEN1, genetic screening was preformed and germline mutation was detected in menin gene (1649 insC). LOH in tumor tissues (parathyroid gland and breast) is in course. Screening for BRCA1/2 was advised. Primary hyperparathyroidism still remains indicating the presence of multiglandular disease and total parathyroidectomy is planned. Plasma chromogranin A level is increased.
We presented a patient with MEN1 and breast cancer. Owing to our knowledge, Honda *et al*. described a MEN1 patient with parathyroid adenoma and breast cancer, lacking a family history. A germline MEN1 mutation was detected, as well as LOH at 11q13 in both tumors. The authors suggested that the clinical spectrum of MEN1 might also include breast cancer.

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P300

Congenital TBG production disorder

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Introduction
We describe the case of 35-year-old man in whom laboratory abnormalities in thyroid function were observed by chance.
Case report
For the first time, the patient was examined in the local Department of Internal Medicine because of pre-arthroscopy examination in March 2002. Low level of total thyroid hormones (T_3 0.76 nmol/l and T_4 48.0 nmol/l) was observed by chance, while TSH value was normal (2.37 mIU/l). The patient did not suffer from any clinical symptoms, and the ultrasound scan showed a normal finding. It was thought about the central hypothyroidism and the patient was sent to MR of hypophysis where no pathology was found. The thyroxine substitution of low doses (50 μg/day) was medicated. The hormonal substitution was gradually increased to doses of 200 μg thyroxine/day. To endocrine ambulance the patient was sent in December 2005 for the first time. A low level of TSH and high level of free thyroid hormones was found. The patient was without clinical symptoms. We examined the function of hypophysis and it was normal. We recommended to discontinue the substitution, and the next examination showed normal level of TSH, while the level of total thyroid hormones remained low.
Conclusion
We closed the case with the diagnosis of TBG-binding capacity defect where the production disorder is congenital. These are laboratory changes without clinical significance. The diagnosis was confirmed by the level of TBG which was undetectable.
In practice, it is necessary take this defect into account because of the potential development of hyperthyreosis factitia caused by prolonged medication of the thyroxin substitution where the congenital TBG production disorder was not recognized. In differential diagnosis, it is necessary to rule out the central hypothyroidism.

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P301

Ectopic lingual thyroid gland: two case report

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Aim
Thyroid tissue originates from foramen cecum located in the base of the tongue and with embryonal development it descends through thyroglossal duct to its normal location. A total or partial failure in thyroid tissue descending causes ectopic thyroid tissue. One of this ectopic region is lingual region. We presented two case of ectopic thyroid tissue.
Case 1
A 18-year-old female that uses levothyroxine 100 mcg/day for hypothyroidism admitted to endocrinology policlinic. In laboratory investigation TSH and free T_4 values were 2.95 μIU/ml (0.4–4.2 μIU/ml) and 1.25 ng/dl (0.8–2.7 ng/dl) respectively. In thyroid ultrasound there was no thyroid tissue echogenity on normal thyroid location, but there was $13\times21\times35$ mm thyroid echogenity located midline in the superior of thyroid cartilage. Thyroid scintigraphy that performed with 3 mCi Tc^{99m} pertechnetate confirmed the thyroid tissue in sublingual region that showed in ultrasonography.
Case 2
A 24-year-old women admitted to endocrinology policlinic with puffiness of neck and dyspnea. Laboratory values were as follow: TSH 7.99 uIU/ml, free T4 0.78 ng/dl. In thyroid ultrasound we did not detect thyroid tissue in normal location but $16\times21\times26$ mm nodular tissue was detected in right sublingual region. In Scintigraphy performed with 3 mCi Tc^{99m} pertechnetate there was no uptake in normal region but there was a focal activity in sublingual region. We prescribed levothyroxine and patient is on follow-up.
Conclusion
Ectopic thyroid tissues may be anywhere in embryonal descending route but rarely seen in mediastinum, heart, esophagus, or diaphragm. The most frequent location of ectopic thyroid tissue is at the base of tongue, accounting for about 90% of the reported cases. Clinical findings are related to size of ectopic tissue and include dysphagia, dysphonia, and dyspnea. In 70 % of patients lingual thyroid tissue is the only thyroid tissue and one third of this patients have hypothyroidism. We suggest screening other possible regions for ectopic thyroid tissue if thyroid tissue is not detected in normal anatomic location.

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P302

An unusual case of diabetes mellitus as a result of heterozygous missense mutation R482W in LMNA gene (familial partial lipodystrophy type 2), described for the first time in Russian population

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Background
Familial partial lipodystrophy type 2 (Dunnigan syndrome and FPLD2) is a rare genetic disorder, associated with different metabolic abnormalities, especially insulin resistant diabetes mellitus, dyslipidaemia, hepatic steatosis, and cirrhosis, cardiovascular disease, and cardiomyopathy, kidney disease.
Clinical case
A 20-year-old patient first presented with changed appearance due to abnormal subcutaneous fat tissue redistribution (lipodystrophies in limbs and abdomen and lipohypertrophies of face and neck), acanthosis nigricans, history of diabetes mellitus since the age of 18, with significant insulin resistance (insulin daily dosage up to 200 U and combined therapy with no effect). Despite different therapeutic strategies, glycemic control was poor: HbA1c 15.4% (individual target level is 5.5%), glycemic levels during the day 13.0–25.0 mmol/l (individual target levels are 5.0–7.0); ALAT 222 U/l (10–40), ASAT 149 U/l (10–40), total cholesterol 452–mg/dl (<175), triglycerides 953 mg/dl (<150), LDL 222–mg/dl (<100), HDL 40 mg/dl (>48), immunoreactive insulin 49 mcm/ml (5–25), leptin 6.4 ng/ml (3.7–11.1). In US scan there were signs of hepatic steatosis, hepatomegaly, and splenomegaly. Hypercorticism and acromegaly were excluded. All those clinical signs and family history of specific changed appearance, diabetes and PCOS in many women (aunts, cousins) in patient's family led us to the clinical diagnosis of FPLD2, which was confirmed genetically by sequencing of *LMNA* gene and revealing heterozygous missense mutation R482W, previously described in FPLD2 (1). As previous symptomatic combined hypoglycemic and hypolipidemic treatment showed not enough efficiency, we now plan to start metreleptin therapy, recently approved for inherited lipodystrophies treatment by FDA, as soon as it will be registered in Russian Federation.
Conclusion
Poorly controlled and difficult to manage diabetes mellitus especially in young age may be a result of a rare inherited condition. This is the first family with FPLD2 due to *LMNA* mutation described in Russian population, which provides a key for further studies of this pathology in Russian Federation.
(1) Shackleton S. 2000 LMNA, encoding lamin A/C, is mutated in partial lipodystrophy. *Nature Genet*. **24** 153–156.

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P303

A patient with lung ectopic parathyroid coexistent with primary hyperparathyroidism and end-stage renal diseases

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We report the case of 57-year-old man with end-stage renal disease, primary hyperparathyroidism and after an surgery of upper parathyroid glands with ectopic parathyroid localized in lung. Patient was directed to our hospital to perform diagnostics on hyperparathyroidism. Two years earlier (2011) patient was hospitalized because of weakness and weight loss, and was diagnosed with primary hyperparathyroidism. In 2012 he underwent the bilateral parathyroidectomy of upper glands which resulted in a reduction of PTH to correct values. Patent was repeatedly dialyzed just before the surgery because of renal failure. After the surgery patient was qualified to chronic dialysis because of end-stage renal disease. In 2012 during the hospitalization due to pneumonia, tumor in right upper lobe has been revealed in X-ray and CT of chest. Laboratory tests showed gradual re-increase of PTH. The neck CT did not show presence of parathyroid gland. MIBI parathyroid scan did not reveal any focus of increased uptake of radioisotope marker as well. Patient declared back pain escalating in sitting position. Laboratory tests revealed hypercalcemia, correct level of plasma phosphate and increased level of PTH- 3094 pg/ml. Chest CT scan was made once again and larger nodule in lung was found. Its intense uptake after contrast perfusion indicated high risk of neoplasmatic process. Owing to suspicion of lung neoplasm and bones pain, the bones scintigraphy was made as well, but it did not reveal traits specific to metastasis or brown tumor. Pulmonary nodule presented in MIBI-SPECT-CT showed increased uptake of radioactive marker which suggested neoplasmatic process. Considering clinical symptoms raising the probability of PTH secretion by the lung tumor and its growth, the patient was qualified for surgery. Intraoperative histopatology examination did not reveal malignant neoplasmatic lesion. PTH level lowered to 166.7 pg/ml.

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P304

Graves–Basedow disease in adolescent patients with type 1 diabetes mellitus

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The prevalence of GD (Graves–Basedow disease) in adolescents with T1DM (type 1 diabetes mellitus) is around 0.5%. Most often the diagnosis of GD in T1DM patients is made many years after the onset of T1DM. The present clinical case describes an adolescent with GD and T1DM and highlights how difficult the management of this disease can be. 17-year-old male was referred to our Department for reevaluation of Graves–Basedow disease. Patient suffered from T1DM for 14 years, with unsatisfactory metabolic control (HbA1c 9.17%). Moreover in 2009 he was diagnosed with Hashimoto's thyroiditis (elevated thyroid antibodies), however remained euthyroid. In September 2011 patient was diagnosed with hyperthyroidism and treated with methimazole (MMI) to maintain euthyroidism. 2 months before the referral, a trial period off medication had been attempted, but the patient experienced a return of symptoms (fatigue, palpitations, and heat intolerance). Family history was significant for autoimmune thyroid disease and T1DM in his mother. On physical examination, the patient had a heart rate of 110 b.p.m., BP of 130/70 mmHg. There was no evidence of ophthalmopathy. Thyroid examination revealed enlarged thyroid gland. Laboratory funds showed recurrence of hyperthyroidism (TSH <0.004 μU/ml, fT_4 36.76 pmol/l). After discussing both therapeutic options with parents (MMI treatment continuation or radioiodine ablation) the patient was administered I-131. Within 2 months of radioiodine therapy, hypothyroidism was achieved, and the patient started thyroid hormone replacement. Three months after definitive therapy, the patient reported improved school performance, decreased fatigue and no abnormalities in heart rhythm. Diabetes metabolic control did not alter during the treatment.

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P305

Follicular thyroid carcinoma presenting with occipital bone and lung metastasis

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When follicular thyroid carcinoma (FTC) is diagnosed, 25% of the patients extrathyroidal invasion, 5–10% lymphatic metastasis and 10–20% distant metastasis are determined. The most common site of distant metastases of FTC is the lung, followed by the bone. The incidence of skull metastasis of FTC is about 2.5–5.8%. Skull metastasis of FTC was located in the skull base and occipital area.
Case
A 60-year-old man admitted at 2006. He was operated for total thyroidectomy at 1998. Histopathology of the surgical specimen was reported as follicular carcinoma of thyroid with features of vascular invasion. 150 mCi of I-131 was given. I-131 whole-body scanning (^{131}I-WBS) after treatment was normal. When the patient admitted to our center, ^{131}I-WBS was performed. It revealed occipital bone and lung metastasis. The patient was operated and occipital bone removed. Histopathology of the surgical specimen was reported as FTC metastasis. 200 mCi additional radioiodine dose was given in 2006. In 2008, 250 mCi additional radioiodine dose was given for recurrence. ^{131}I-WBS revealed occipital bone and multiple defined mass, which were metastasis in both lungs in

September 2012. Cranial MR revealed 24×24×22 mm mass in occipital zone. He underwent F-18-FDG PET/CT scan for investigating distant metastasis. On PET scan, an increased of F-18-FDG (SUVmax: 24.1) uptake was seen 23 mm mass which had destructed occipital bone. Also, increased FDG uptake (SUVmax: 10.8) 26 mm mass upper lobe anterior segment in the right lung and 340 mm mass middle lobe medial in the right lung (SUVmax: 2.4) was showed. There were multiple parenchymal lesions, which were in different diameters and in different metabolic activities in both lungs. The patient was given 275 mCi additional radioiodine. The treatment of choice of FTC is total thyroidectomy with radioiodine administration, surgical procedure for metastatic lesion and TSH suppressive therapy.

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P306

Long-term use of tolvaptan in hyponatraemia due to SIADH in elderly

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Background
Hyponatraemia is the most common electrolyte disorder seen in clinical practice. Even mild hyponatraemia can lead to gait disturbances and cognitive dysfunction in the elderly.
Case history
A 83-year-old lady presented to acute admission unit with worsening of confusion. Her background medical history includes chronic obstructive pulmonary disease for which she is on inhalers. She was also having hyponatraemia for the last 3 years manifesting with recurrent falls and confusion resulting in recurrent prolonged hospital admissions.
Her blood and urine investigations were consistent with syndrome of inappropriate ADH secretion (SIADH). She was thoroughly investigated for any underlying cause for her SIADH and was negative. During her previous admissions she was tried on fluid restriction, demeclocycline, hypertonic saline, and diuretics resulting in variable temporary response. She was also tried on short term tolvaptan on two previous occasions resulting in temporary improvement of her serum sodium and symptoms but relapsed.
During her current hospital admission she was confused with mini mental state examination (MMSE) of 16/30. She was commenced on tolvaptan (vasopressin receptor antagonist) and her sodium normalised. Her confusion improved with MMSE of 26/30 at discharge. Her serum sodium levels remained in normal range 12 months after discharge on tolvaptan. She has not had any further falls and her cognitive function remains good including her quality of life.
Conclusion
Hyponatraemia due to SIADH is common in elderly patients. The most effective treatment for chronic hyponatraemia due to SIADH is the use of vasopressin receptor antagonists which selectively increase solute free water excretion by kidneys. This case highlights that careful selection of patient for treating with tolvaptan will be cost effective in treating SIADH on long-term basis preventing prolonged hospital stays and regaining their independence.

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P307

Challenges in exophthalmia management: Frontal mucocele

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Frequently seen in connection with thyroid disease, exophtalmic syndrome has a much large spectrum of differential diagnosis including numerous local and general aetiologies. Conditions such as mucoceles of paranasal sinuses don't have always nasal or sinus symptoms but may present with ophthalmological manifestations.
A 50-year-old woman presented for a 2-months history of right eye proptosis with upper eyelid swelling, periorbital pain, occasionally diplopia, general sweating, and 5 kg weight loss. She didn't report fever. Medical history included hypertension, dyslipidemia, and 3rd degree obesity. Physical examination revealed asymmetrical exophthalmia (Reye 22 mm and Leye 18 mm), chemosis, periorbital tissues swelling, especially of the upper eyelid, decreased ocular mobility, and diplopia on downward gaze. Intraocular pressure was 22 mmHg for the Reye and 16 mmHg for the Leye. Fundoscopic examination was normal. The thyroid function was normal. TRAbs were borderline (1.6 U/l) while TPOAbs were positive (163 U/l). Her white blood cell count was normal ($8.01\times10^3/mm^3$) but sedimentation rate was slightly elevated (26.9 mm/h). Cranial CT scan showed asymmetrical exophthalmia (Reye 22.9 mm and Leye 19.2 mm) and an extensive cystic lesion, 35/18 per 30 mm diameter, originating in the frontal sinus with extension in the upper extremity of the right orbit, exerting mass effect on the superior oblique muscle, the medial rectus, and the right lacrimal gland. She developed acute inflammation (despite lack of systemic involvement) of the right orbital content (cellulites) which triggered rapid admission in ENT department. During surgery, acute sinusitis of the right maxillary, sphenoidal, ethmoidal, and frontal sinuses was observed. Treatment included surgical drainage under general anaesthesia with good post-operative recovery and minimal residual swelling.
In a patient with exophthalmic syndrome, rare causes such as sinus mucocele should be considered. Early recognition and treatment are very important in preventing orbital complications and avoid visual loss.

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P308

Testicular histological and immunohistochemical particularities in a post-pubertal patient with 5α-reductase type 2 deficiency

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Introduction
Testicular morphology and immunohistochemistry have never been reported in genetically documented adult patients with 5α-reductase type 2 deficiency (5α-R2 deficiency).
Case report
We describe the testicular histopathology of a 17-year-old XY female with primary amenorrhea, failure of pubertal breast development, virilization, clitoromegaly, and bilateral cryptorchidism (testes located in the inguinal canals). The diagnosis of 5α-R2 deficiency was confirmed by the recurrent homozygous Gly115Asp loss of function mutation of the *SRD5A2* gene. We performed an immunohistochemical analysis in order to further study the relationship between seminiferous tubules structure, Sertoli cell differentiation and androgenic signaling impairment in this case. We evaluated the testicular expression of the anti-Müllerian hormone (AMH) , androgen receptor (AR), and 3β-hydroxysteroid dehydrogenase (3βHSD). Histological analysis revealed a heterogeneous aspect with a majority (92%) of seminiferous tubules (ST) presenting a mature aspect but containing only Sertoli cells and devoid of germ cells and spermatogenesis. Focal areas of immature ST (8%) were also found. Testicular AR and 3βHSD expression were detected in adult male control, 5α-R2 deficiency and CAIS subjects. However, AMH expression was heterogeneous (detectable only in few AR negative prepubertal ST, but otherwise repressed) in the 5α-R2 deficiency, conversely to normal adult testis in which AMH was uniformly repressed and to an adult CAIS testis in which AMH was uniformly and strongly expressed.
Conclusion
Intratesticular testosterone can repress AMH by itself, independently of its metabolism into dihydrotestosterone. We also confronted our results to the few post pubertal cases of 5α-R2 deficiency with available histological testicular description, reported in the literature and interpreted histological findings, in the more general context of evaluating the fertility potential of these patients if they were raised as males and were azoospermic.

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P309

Treatment of hyponatraemia with vasopressin receptor 2 antagonists (V2RA): case series

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Vasopressin receptor 2 antagonist (V2RA) provide treatment option for patients with hyponatraeamia in the context of syndrome of inappropriate antidiuretic hormone secretion (SIADH).

We report the results of seven patients (six males, one female, average age 65.7) with hyponatraemia secondary to SIADH treated with V2RA (Tolvaptan) in years 2011–2013. Six patients had underlying diagnosis of lung cancer, one patient was diagnosed with sarcoidosis. Four patients died due to their underlying disease, three patients remain under the continuing follow-up.
To exclude other causes of hyponatraemia we checked, thyroid function, plasma, and urine osmolalities, urinary sodium, cortisol level, and performed short synacthen test. The initial treatment was fluid restriction. Three patients (42.86%) were transiently treated with demeclocycline, subsequently switched to V2RA. V2RA doses varied with total weekly doses between 35 and 75 mg.
The average sodium concentration before commencing V2RA treatment, was 121.74±5.09 mmol/l (range 112–126 mmol/l). The average correction time of hyponatraemia was 9.28 days. The sodium levels were corrected on average by 14.86±6.41 mmol/l. The average rate of correction was 4.1 mmol/day (range 0.44–11 mmol/day).
Patients were followed for average of 237.8 days. Total time of follow-up was 1665 patient-days. Patients' renal function and electrolytes were monitored. We obtained following results, pre- and post-V2RA use: creatinine 82.67 vs 83.67 umol/l (+1.21%), urea 5.13 vs 7.23 mmol/l (+40.9%), potassium 4.45 vs 4.08 mmol/l (−8.24%). Monitoring of liver function tests (LFTs) revealed following pre- and post-V2RA average levels of aspartate transaminase 44.8 vs 43.2 IU/l (−3.7%), alanine transaminase 31.5 vs 32.3 IU/l (+2.65%) and total bilirubin 16.3 vs 14.0 umol/l (−14.29%) respectively.
Our case series gives evidence for effective use of V2RA in the treatment of hyponatraemia in context of SIADH without excessively rapid hyponatraemia correction or significant changes in levels of creatinine, potassium, and LFTs.

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P310

Do clinical events always suggest familial form of medullary thyroid carcinoma (MTC)? – two case reports

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Introduction
MTC originates from the parafollicular calcitonin secreting cells. One quarter of MTC patients have familial form of the disease with RET mutation.
Case reports
First female patient underwent total thyroidectomy for MTC at the age 40. Further investigation showed elevated urinary catecholamine levels and MIBG scintiscan verified bilateral pheochromocytoma. Bilateral adrenalectomy was performed. On follow-up basal and stimulated calcitonin levels, serum levels of metanephrine, normetanephrine, and parathyroid hormone were normal. Since the mother of our patient had bilateral pheochromocytoma, genetic testing was done. It revealed RET 634 codon mutation in our patient, her 67 years old mother and her 12 years old daughter. Further examinations showed the mother of our patient had MTC and primary hyperparathyroidism, and she was operated on. Daughter of our first patient had elevated basal and stimulated calcitonin levels along with c634 RET mutation and total thyroidectomy was done. She had not developed hyperparathyroidism and pheochromocytoma up to now. Pathologic analysis proved multicentric MTC in all patients.
Our second female patient underwent total thyroidectomy at the age 57 on the grounds of non-functional nodules in the thyroid, with elevated calcitonin and CEA levels. Total parathyroidectomy with implantation of one parathyroid gland in sternocleidomastoid muscle was done, due to primary hyperparathyroidism. Histology proved MTC and hyperplastic parathyroids. She had a tumour in the left adrenal gland, with preserved adrenal function, and negative MIBG scintiscan and PET scan. On the control basal and stimulated calcitonin levels and CEA were in reference range. Slightly increased chromogranin A persists. Genetic testing did not find positive RET mutation.
Conclusion
Genetic screening for RET mutations is extremely helpful in finding familial forms of malignant tumours and reducing mortality in hereditary MTC, particularly since MTC in RET positive children is most commonly occult at the time of screening.

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P311

A rare case of cutaneous metastization of a differentiated thyroid carcinoma initially diagnosed as Hurthle cell adenoma

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Introduction
Cutaneous metastization of differentiated thyroid carcinomas is a rare event.
Clinical case
MMS, a 69-year-old male was submitted to left hemithyroidectomy+ isthmectomy on May 2006 after FNA of a left node revealed follicular tumor. Histology showed Hurthle cell adenoma. The patient maintained irregular follow-up by endocrinologist. In October 2011 he referred the appearance of small bilateral cervical skin nodules. Physical exam showed three subcutaneous, 4 mm diameter, nodules, and a 7 mm diameter lymph node. Ultrasonnography of thyroid and cervical soft tissues was reccomended. The patient returned to the endocrinologist in October 2012, referring increase in size of the cervical nodules, which was confirmed by physical examination. A FNA was requested, having revealed 'cytological and immunohistochemical findings compatible with the diagnosis of Hurthle cell follicular tumor. Clinical and imageological correlation was suggested to differentiate between lymoh node metastasis of Hurthle cell follicular tumor or tumor recurrence. Paraffin blocks used in 2006 were recovered and examined by a different pathologist. Histology showed, in addition to a papillary carcinoma, histological findings compatible with thyroid oxiphyl (Hurthle cell) neoplasm. On the three examined blocks no unequivocal images of capsule or vascular invasion were observed, turning it impossible to differentiate between adenoma and Hurthle cell carcinoma.
Thyroidectomy totalization and extenal nodules removal were performed. Histologycal exam revealed 'oncocytic cell carcinoma, occupying extrathyroidal tissues with venous and lymphatic invasion. In the nodules an identical neoplasm is observed, that invades skeletal muscle. There is TTF1 and thyroglobulin expression. In conclusion: extensively invasive oncocytic cell (follicular) carcinoma'.
This clinical case constitutes an uncommon example of cutaneous metastization of a differentiated thyroid carcinoma and highlights the importance of a correct differential diagnosis between Hurthle cell adenoma and carcinoma.

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P312

Diagnosis of neonatal diabetes mellitus in the mother through the detection of hyperglycemia in her child

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Introduction
Neonatal diabetes mellitus (NDM) is a rare disease diagnosed within the first months of life that is usually permanent in 50% of cases. Heterozygous mutations of *KCNJ11* and *ABCC8* genes encoding the two Kir6.2 and SUR1 subunits of the b-cell ATP-dependent potassium channel have been associated with NDM, which is characterized by a successful response to sulfonylureas.
Case report
We present a 32-year-old woman diagnosed with type 1 diabetes. She was born at 37 weeks (weight: 2900 g) and presented with diabetes onset at 3 months. Since onset she has been treated with insulin and has presented as poorly controlled. She began treatment with CSII for planning pregnancy and presented an acceptable metabolic control during pregnancy (HbA1c 6%), which finalized at 37 weeks by eutocic delivery. The neonate (weight: 2750 g and height: 48 cm) developed hyperglycemia from the 24th hour of life that required insulin. Genetic studies requested in both patients detected a heterozygous mutation in the *KCNJ11* gene (p.Arg201His, c.602G> A). Evaluation of glycemic control (including CGMS) and assessment of pancreatic reserve before switching from insulin to sulfonylureas, and again after 6 months, were performed.
Results
We observed an improvement in both glycemic control and pancreatic reserve with sulfonylureas in the mother, although she needed high doses (0.8 mg/kg per day). In the child good glycemic control as well as improvement of pancreatic reserve were also achieved and we completely stopped insulin on the third day after start of sulfonylureas, requiring downstream dose (0.2 mg/kg per day).

Conclusions
The onset of NDM due to a mutation of *KCNJ11* in the first days of life is exceptional, also the association to not low birth weight. Most patients with NDM respond to treatment with sulfonylureas, but the response may vary. It is essential to reconsider the diagnosis of type 1 diabetes in patients with disease onset before 6 months of life.

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P313

Ectopic co-secretion of growth hormone and growth hormone-releasing hormone from a neuroendocrine lung tumor in a patient with MEN1 syndrome

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The co-secretion of GHRH and GH has been described previously in a patient with GHRH producing pituitary somatotroph adenoma. Here we present a patient with MEN1 and ectopic secretion of both GHRH and GH from a neuroendocrine lung tumor.
A 52-year-old woman was diagnosed in 2009 with two lung tumors, 4 cm right upper lobe tumor, and 2 cm left lower lobe tumor. Owing to a mild coarsening of facial features, acromegaly was suspected. Endocrine studies showed lack of GH suppression during oGTT, increased serum levels of IGF1, GHRH, and Chromogranin A, suggesting ectopic acromegaly. Pituitary MRI showed hyperplasic pituitary. Octreoscan revealed avid take-up of tracer in the right lung tumor only. The patient underwent two consecutive thoracic surgical procedures. Both tumors were characterized as well-differentiated neuroendocrine carcinomas of primary pulmonary origin. The left sided tumor showed no GHRH, GH, or ghrelin immunoexpression. The right sided tumor stained positive for both GHRH and GH. All GH positive cells were positive for GHRH receptor as well. Postoperative Octreoscan was negative, neuroendocrine tumors normalized. Normal IGF-1, GH suppression during OGTT, immeasurable GHRH, and pituitary shrinkage, confirmed ectopic acromegaly. The patient was later diagnosed with nonfunctioning hyperplasia of the left adrenal gland, and primary hyperparathyroidism. Analysis of *MEN1* gene revealed Arg355Trp mutation in exon 8 of the *MEN1* gene.
To our knowledge, this is the first case describing ectopic secretion of both GHRH and GH from an extracranial tumor. The presence of GHRH receptor on GH positive cells may suggests possible autocrine/paracrine effect of GHRH on GH synthesis and/or secretion in neuroendocrine tumor cells.

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P314

Refractory Graves' ophthalmopathy treated with rituximab

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Introduction
Graves' ophthalmopathy (GO) is common in the course of Graves' disease, but optic neuropathy is present in only ~5% of patients with GO. We present a case of recalcitrant Graves' orbitopathy with late development of neuropathy, satisfactorily treated with rituximab.
Case report
A 50-year-old female smoker was referred to our department for further management of Graves' disease with associated GO. She complained of worsening eyelid edema, intermittent vertical diplopia, and pruritic eyes for several months prior, but diagnosis remained elusive due to the predominance of eyelid swelling and inconspicuous hyperthyroid symptoms.
On presentation she had disfiguring eyelid edema, bilateral exophthalmos (24/110/24), mild diplopia, normal visual acuity, color perception, and fundoscopy. CAS score was 5/7, with moderate severity. She received i.v. pulse methylprednisolone for 3 months to a cumulative dose of 6 g with improvement in CAS to 3/7. Standard orbital radiotherapy was delivered 3 months later, with minor improvement of disease activity.
Thyroid status stabilized on a combination of methimazole plus adjunct lithium, permitting an uncomplicated thyroidectomy 2 months later.
However, visual acuity declined in the course of the above treatments to 'hand motion', necessitating 'salvage' rituximab infusions twice, at 375 mg/m^2. CD20 depletion was immediate and sustained after 6 months, but thyroid-stimulating immunoglobulin titers remained high throughout. 6 months after treatment CAS is 1/7, color vision is improved and visual acuity measures 4/10 bilaterally.
Conclusions
i) GO may not be readily recognized if any particular feature prevails in the clinical picture.
ii) Optic neuropathy can develop after GO treatment, despite improved disease activity and in the presence of normal disc appearance.
iii) Late administration of rituximab after established anti-inflammatory therapy may still benefit vision.

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P315

Drug induced skin eruption in type 2 diabetes mellitus patients who treating with a dipeptidyl peptidase-4 inhibitor plus metformin

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Background
Incretin-based therapy is increasingly used in the management of type 2 diabetes mellitus. Although dipeptidyl peptidase-4 inhibitors (gliptins) are well tolerated, side effects can be observed in various body systems. Here we report three cases of drug-induced skin eruption with strong itching of the gliptins plus metformin combination therapy.
Case reports
A 59-year-old woman and a 57-year-old man, who had been using vildagliptin plus metformin for 2 and 6 months respectively admitted to our institution with allergic skin lesions. A 61-year-old man with type diabetes who had been using sitagliptin plus metformin for 3 months, admitted to our institution. Their physical examination indicated good general condition, with no pathological findings except for the skin eruptions. Skin lesions appeared on their chest, abdomen, arms, and legs that hyperemic, erratic, erupted, and pruritic. Patients had no history or evidence of autoimmune, neoplastic, or infectious diseases. The combined treatment was discontinued in patients. Patient 1 switched to metformin plus nateglinide, patient 2, and 3 to metformin plus gliklazid. After withdrawal of the gliptin plus metformin combination, there was a significant improvement of eruption. None of the patients treated with prednisolone. Complete remission was achieved 8, 10, and 7 weeks after discontinuation of gliptin plus metformin respectively.
Conclusion
Skin lesions in patients went into remission despite further metformin administration. We suggest that in our patients development of allergic reaction of skin was due to gliptin alone. Although skin eruption due to gliptin is rare, it is a considerable complication. Despite its unknown mechanism, this reaction should be considered in patients using gliptin. More observation is required over a period of time to clarify use of this class of drug.

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P316

Severe postmenopausal virilization of unknown origin

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Introduction
The severe course of hyperandrogenism during the menopausal transition requires the exclusion of androgen-secreting tumors.
Case report
A 60-year-old postmenopausal woman was referred to the Department of Endocrinology with a 3-year history of progressive development of hyperandrogenism with virilization (severe hirsutism, frontal balding, deepening of voice, increased muscle mass, and secondary polycythemia).

Hormonal evaluations revealed serum testosterone level in the male range (9.1–11.2 ng/ml), with decresed gonadotrophins and estradiol concentration characteristic of a follicular phase (107–117 pg/ml). Levels of androstenedione, DHEA-S, prolactin, cortisol, CA-125, and α-fetoprotein were normal.
Although initial imaging procedures (abdominal CT, pelvic MRI, and transvaginal ultrasound) failed to reveal the source of androgens synthesis, total hysterectomy and bilateral salpingo-oophorectomy was performed. Histopathological examination showed no pathological changes; however, testosterone level decreased significantly following the surgery (1.3 ng/ml) but did not achieve the female range (0.1–0.8 ng/ml). The patient showed significant regression of clinical signs and symptoms of hyperandrogenism, including the need of phlebotomy due to polycythemia.
Conclusions
The differential diagnosis of hyperandrogenism and virilization in postmenopausal women is challenging and requires well-considered clinical management due to the small size of ovarian androgen-secreting tumors.

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P317

Propylthiouracil induced lupus erythematosus in a patient with Grave's disease: a case report

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Introduction
Drug-induced lupus erythematosus (DILE) is a variant of systemic lupus erythematosus that resolves within days to months after withdrawal of the drug, in a patient with no previous history of SLE.
Case report
A 60-year-old female presented at Mother Teresa Hospital with toxic multinodular goiter. She received treatment with propylthiouracil and atenolol for a month, and she developed symptoms like malaise, muscle pain, shortness of breath, cough, nausea, vomiting, and gastric pain. The laboratory tests revealed elevated thyroid function, elevated transaminases, and pancytopenia. Abdominal ultrasound was normal. Bone marrow aspiration resulted normal. Positive direct and indirect Coombs tests confirmed the immune-mediated cause of pancytopenia, and suspicions were raised towards a drug-induced mechanism. Under these circumstances PTU was discontinued and the patient was started on prednisolone. The next day the patient complained of left hip pain, breath shortness, and the appearance of mouth ulcers. Thoraco-abdominal CT scan revealed pleural effusion, splenomegaly, and coxarthritis sinister. Antinuclear antibodies resulted positive (+++), C_3=121 (79–152), C_4=14.7 (16–38). Prednisolone dose was raised. A week after, her condition improved and the blood tests started to normalize. Methimazole was started and the patient observed for adverse effects. After a year she continued on methimazole and her serologic markers resulted within ranges.
Discussion
DILE can arise months to years after exposure to drugs prescribed to treat various medical conditions. Literature describes cases where antithyroid drugs induce autoimmune disorders. The recognition of this side effect of antithyroids is important for the early interruption of the drug, which would lead to an improvemet of the situation, and avoid unnecessary tests and treatments.

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P318

Monomorphic ventricular tachycardia due to primary hyperparathyroidism: a case report

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Introduction
Cardiovascular changes are rare but life-threatening consequences of primary hyperparathyroidism.
Case report
A 53-year-old man, with past and family history of peptic ulcer, presenting with coronary heart disease and ischemic and dilated cardiomyopathy, treated with cardiac resynchronization. He was admitted to the emergency room due to sustained monomorphic ventricular tachycardia (MVT). Laboratory tests revealed primary hyperparathyroidism (parathyroid hormone 1020 pg/ml and calcium 18.5 mg/dl), acute renal failure and hipocalemia. To correct hypercalcemia, pamidronate, furosemide, and hydrocortisone were started. Besides, he was treated with amiodarone, lidocaine, magnesium sulphate, isosorbide dinitrate, clopidogrel, aspirin, and enoxaparin. Multiple MVT episodes alternated with sinus rythm before stable conversion was achieved. He was transferred to the cardiac intensive care unit, where renal replacement therapy was started for faster hypercalcemia correction. Parathyroid ultrasound revealed a solid mass posterior and below to the left thyroid lobe, suggestive of parathyroid adenoma and parathyroid scintigraphy showed a hyperfunctioning mass in the left and inferior parathyroid gland. A parathyroidectomy of the left and inferior parathyroid gland was performed, with subsequent restoration of calcium levels to normal. The anatomopathologic exam confirmed parathyroid adenoma diagnosis. Basal endocrine tests also revealed hypergastrinemia (nineteen times the normal levels), high levels of chromogranin A, urinary metanephrines and hydroxyindolacetic acid. Esophagogastroduodenoscopy showed peptic ulcer in the less curvature of stomach and the anatomopathologic exam revealed non atrophic gastritis and was positive to *Helicobacter pylori*. An octreoscan was requested but the patient refused to do it.
Discussion
Undiagnosed hyperparathyroidism with important hypercalcemia in a compromised heart can trigger life-threatening ventricular arrhythmias. The hypercalcemia arrhythmogenic effect could be related to early or delayed afterdepolarizations and shorten of the effective refractory period. Primary hyperparathyroidism together with the patient's past and family history of peptic ulcer and hypergastrinemia suggest a multiple endocrine neoplasia type 1 syndrome.

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P319

The unusual case of the appearance of radioiodine (I-131) uptake in lung metastases in a patient with papillary thyroid cancer (PTC)

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A 67-year-old male with PTC (pT3N0) underwent a total thyroidectomy in February 2004. Subsequently he was treated with I-131 and radiotherapy (RT). Combined therapy did not normalize the serum thyroglobulin (TG). Because of elevated TG and persistent I-131 uptake in thyroid bed the patient received a total activity of 21275 MBq of I-131 in 4 years. The treatment was stopped in March 2007 due to a lack of I-131 uptake in the last post-therapeutic whole body scan (WBS) with still elevated TG. Other imaging studies (chest CT and bone scan) were negative for metastases (mets). Controlled PET-CT with FDG was performed in December 2007 and multiple lung micro-mets were revealed in the CT scan, but without concomitant FDG uptake. PTC lung mets were confirmed in the histopathology. The patient was subsequently treated with I-131 in February 2008. WBS did not reveal I-131 uptake in the lung mets. Moreover, the patient refused treatment with the kinase inhibitor. TG has gradually increased. After an episode of aphasia in October 2013 a head MRI was performed and revealed a right frontal lobe tumor (25 mm – mets or primary). RT to the head was performed followed by I-131. Surprisingly WBS revealed very intense diffuse accumulation of I-131 in the lungs, but not in the frontal lobe.
Conclusions
The case described above raises the question of whether the appearance of radioiodine uptake in lung metastases in 2013 stems from some unknown mechanism or rather the lack of radioiodine uptake in lung metastases in 2007 was caused by contamination with iodine? This is possible but unlikely, since the patient had been treated many times before with I-131 and has always been informed about the principles of avoiding cross-contamination. However, ioduria was not performed in the patient, as this examination is not routinely performed in our country.

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P320

Recurrent debilitating thyroiditis

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Case
A 46-years-old anaesthetist presented with 2 weeks history of general malaise, sore throat, and fever. Symptoms started while on holiday. A diagnosis of subacute thyroiditis was made overseas based on presentation and suppressed TSH level. He was started on betamethasone 4mg and ibuprofen for 2 weeks with rapid symptomatic improvement. He felt well enough to travel back to UK. He then presented to our hospital with recurrent symptoms as above.
Investigation and treatment
On examination he was found to have diffusely enlarged and tender thyroid gland with suppressed THS <0.001 μ/l, raised T4 of 28.2 pmol/l and negative thyroid peroxidase antibodies.
Initial thyroid ultrasound showed diffusely enlarged gland. The technetium thyroid scan supported the diagnosis of subacute thyroiditis with low thyroid uptake (0.08%). He was started on propranolol and diclofenac. His symptoms improved and was discharged. On subsequent review in 2 weeks he had recurrent symptoms. TSH remained suppressed at <0.001 μ/l with elevated T_4 of 24.0 pmol/l. He required increased ibuprofen dose and continuation of propranolol. This was followed by third recurrence within 2 weeks with raised T_4 of 26.0 pmol/l and suppressed TSH. He was started on prednisolone 25 mg for 2 weeks. He then continued to improve. Repeat thyroid ultrasound scan showed recovery of the inflamed thyroid parenchyma, reduced size of both lobes with peripheral increased vascularity due to thyroiditis. His thyroid function then normalized within 8 weeks to TSH 2.03 μ/l, T_4 of 15.3 pmol/l. This patient had significant recurrence of subacute thyroiditis with fluctuating and debilitating symptoms over the course of few month. He required phased retune to work.
Discussion and conclusion
Subacute thyroiditis which is considered to be a viral illness rarely recurs after a complete recovery. Recurrent disease could be debilitating. Prompt assessment, treatment, and follow-up are of paramount. Risks and benefits of antithyroid treatment should be considered on individual basis.

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P321

Hashimoto thyroiditis followed by Grave's disease

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Introduction
Hashimoto's thyroiditis (HT) and Graves' disease (GD) are two auto-immune diseases. They have different phenotypes and are generally believed to share a number of common etiological factors but the mechanisms leading to their dichotomy are unknown. An unusual outcome of HT is the conversion to GD.
A mechanism that might be hypothesized to account for the change from HT to GD is the alteration in the biological activity of TSH receptor Abs from predominantlythyroid-blocking antibodies during the hypothyroid phase to thyroid-stimulating antibodies when GD manifests itself.
Case report
A 14-year-old girl, B H, was seen complaining of clinical hypothyriodism manifestation with enlargement of thyroid gland. The result of thyroid function was, FT4 = 5.6 pg/ml (normal = 6.5–20.5), TSHs = 113 μUI/ml (normal = 0.1–5.0), and anti-microsomal antibody titer was high. She takes levothyroxine 75 μg/day. 6 years after she develops clinical hyperthyroidism manifestation and laboratory tests revealed thyrotoxicosis:TSH <0.001 and FT4 = 30 pg/ml. The biological hyperthyroidism remain without levothyroxine and TRAb was high confirming the diagnostic of Grave's disease. She was treated with neomercazole for 6 months and afterward her thyroid function remained normal without medication.
Conclusion
Grave's disease rarely succeded to Hashimoto thyroiditis and the mecanism leading to this state remain unclear.

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P322

Why obesity is multifactorial? Mixture of genetic predisposition, endocrine dysfunction and environmental factors: a case report

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Introduction
Obesity prevalence is growing every year. In most cases, origin is exogenous, a mixture of sedentary and overeating. However, some patients are trend to develop obesity caused by their genetics and other illness.
Case report
A 62-year-old women with diabetes type 2, anxiety and osteoporosis was remitted to our center for obesity. She had been obese since childhood, with very low level of activity and snacking trend. On physical examination she presented 161 cm of height, 95.2 kg of weight, and BMI of 36.73 kg/m^2 with the remainder examination normal. A low calories diet and physical activity were prescribe. With suspected non-syndrome obesity she was referred to Genetic Unit. A mutation on leptin receptor gene was found: LEPR, insertion-mutation TA-77 pb insTA. Exploring new the patient, we showed that she presented thickening of the lips and fingers. On pituitary study IGF1 elevated was found (358 ng/ml, upper limit for sex and age 204 ng/dl) and FSH and LH elevated, with remaining pituitary axis normal. After 2 h of 75 g glucose-load, a level of 1.85 ng/ml of GH was reached. In cranial MRN empty sella showed. 60 mg of lanreotide, a deep subcutaneus injection each 28 days were prescribed. A scintigraphy octreoscan revealed capture in pituitary. The case was evaluated by Neurosurgery Unit rejecting in this moment surgical treatment cause of no identificated pituitary mass and high risk of CSF leak. To the date, the patient had been loss weight with normalization of GH-axis.
Conclusions
In recent years there had been numerous advances in our understanding of genes that influence obesity, but it is unlikely that their contribution was independent of the numbers environmental factors. The percentage of endogenous obesity is small but it is crucial to identify these patients well as they could benefit from more specific treatments.

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P323

Case study in PTU-induced hepatotoxicity: a retrospective analysis of the key aspects of survivability in PTU-induced hepatotoxicity in adults

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A 20-year-old female patient with Graves' disease was commenced on PTU 50 mg OD in June 2009 because of intolerance to carbimazole. She presented with jaundice within 5 months and was subsequently admitted when she started vomiting 2 months later.
She had tenderness in the right upper quadrant. LFT on admission are alkaline phosphatase 268 μ/l (35–104), gamma glutamyl transferase 148 μ/l (5–36), aspartame transferase 194 μ/l (5–38), Bilirubin 226–μ/l (1–17). Liver biopsy showed cirrhotic appearance with expansion of the portal tracts with bridging fibrosis. PTU was stopped; she had a total thyroidectomy and made a slow recovery.
Studies show that PTU- induced hepatotoxicity clinically present as elevations in serum transaminases, whereas other cases show a cholestatic picture with elevated bilirubin and alkaline phosphatases only. Transient increase in aminotransferases has been observed within the first week of treatment in up to 28% of patients.
Our poster aims to show links between published cases of PTU induced hepatotoxicity in adults, with unusually high or low liver enzymes values. The common trends in survival, recovery and death in patients with PTU induced hepatotoxicity. PTU-induced hepatitis is diagnosed based on the occurrence of liver damage within a few months of initiation of therapy; the study aims to show common aspects of microscopic pathology and to recommend frequent LFT testing in patients using PTU. It also aims to review the American Thyroid Association (ATA) guide lines for PTU use and show that mild elevated of liver enzymes during PTU therapy may be a sign of PTU hepatotoxicity.

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P324

Meningioma in a patient with tall cell papillary thyroid carcinoma

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Tall cell papillary thyroid carcinoma is known to be associated with an adverse outcome, namely with the early development of locally recurrent or metastatic disease. Therefore the administration of therapeutic radioactive iodine is considered absolutely necessary in the management of such patients. A meningioma may occur in a patient with another neoplastic disease, having also been described in patients with thyroid carcinoma.
The aim was to describe the case of a patient who presented with a tall cell thyroid carcinoma and was also found to harbor a meningioma.
A female patient, aged 59, presented with a thyroid nodule measuring 1.8 cm on ultrasound. Diagnostic evaluation involving thyroid hormone measurement, ^{99m}Tc-scanning and fine needle aspiration biopsy revealed the presence of malignancy within a cold nodule. Surgery was performed. Histology revealed the presence of a tall cell thyroid carcinoma. Thereafter, the administration of a therapeutic dose of radioactive iodine was planned. A brain CT scan revealed the presence of a tumor in the area of the left temporal lobe. As tall cell papillary thyroid carcinoma may be associated with metastatic disease, the possibility of metastatic disease within the brain was discussed. In order to exclude the presence of tissue absorbing radioactive iodine in the brain a whole body scan with low dose ^{131}I iodine was performed. The scan confirmed that the tumor was not absorbing radioiodine. Subsequently, a therapeutic dose of ^{131}I was administered. A meningioma may occur in a patient with another malignancy. In the case of a patient with thyroid cancer a meningioma can pose therapeutic difficulties, as it may mimic thyroid cancer metastatic disease in the brain, making specific diagnostic evaluation before the administration of therapeutic radioiodine necessary.

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P325

Hypoglycemia in type 1 diabetes mellitus patient – factual ou factitious?

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Introduction
Factitious hypoglycemia results from surreptitious administration of insulin or insulin secretagogues. It can involve non-diabetic individuals with knowledge of hypoglycemiant drugs, or diabetics manipulating the doses.
Clinical case
A 42-year-old women, type 1 diabetic since the age of 14, on intensive insulin therapy (A1C: 8.5%), was hospitalized for study of recurrent severe hypoglycemia in the last 2 months, despite successive insulin doses reductions. History of depression already treated. Clinical examination: conscious and orientated, refusing inter-personal communication; BP: 144/78 mmHg, HR: 96 bpm, BMI 31.1 kg/m^2. Six hours after admission presented severe hypoglycemia ($<$40 mg/dl), erratic, recurrent, and difficult to revert, needing hypertonic dextrose perfusion (30 and 50%) through central venous catheter for $>$48 h. Several continuous glucose monitoring(CGM) were performed: first with CGMS (marked discrepancies between interstitial and capillary glucose registered); posteriorly with Guardian RT, that revealed lack of sensor registry in nocturnal periods, coincident with abrupt glucose reductions. Complementary evaluations (during hypoglycemia): sulfonylureas (chlorpropamide, glybenclamide, and tolbutamide): $<$0.1 μg/ml; insulin: $>$300 mUI/ml, C-peptide: $<$0.1 ng/ml, proinsulin: $<$0.1 pmol/l, β-hydroxybutyrate: 0.17 mmol/l, anti-insulin antibodies: 16.15 UI/ml ($<$0.4). A prolonged fasting test was performed, without any spontaneous hypoglycemia. It was noticed that severe hypoglycemia was preceded by family visits, absences from the infirmary or after visits to the bathroom. After patient confrontation with laboratorial data and psychiatric therapeutic adjustment, the ambulatory insulin scheme was resumed. She was discharged 2 weeks later, much more communicative, and stabilized clinical situation. The patient was reevaluated, 1 month later, and didn't report any severe hypoglycemia.
Conclusion
The provided patient information didn't match with laboratory results, pointing to a factitious disease; CGM records were also discrepant. The triad composed by hypoglycemia, inappropriate high insulin, and low C-peptide, suggested factitious hypoglycemia. The confirmation of this diagnosis requires an exhaustive evaluation and often hospitalization. In diabetics, difficulty is increased and long-term prognosis becomes unpredictable.

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P326

From hemoptysis to diagnosis of congenital hypothyroidism: a diagnostic pitfall

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Introduction
Congenital hypothyroidism (CH) is the most common congenital endocrine disorder. It occurs in Europe with an incidence of 1:3000–1:4000.Thyroid dysgenesis – agenesis, hypoplasia or ectopy – is responsible for 80–90% of CH cases. An ectopic thyroid gland is an uncommon inborn anomaly and is typically located along the thyroglossal duct. To date only few cases of CH due to lingual thyroid diagnosed in adulthood were reported in the literature.
Case report
A 31-year-old man was admitted to the Department of Pulmonology with hemoptysis without cough. Bronchofiberoscopy did not provide the explanation of the reason for hemoptysis. The CT scan of the chest revealed multiple small nodules in both lungs. Suspicion of metastasis to the lungs has been raised. The patient was referred for PET–CT, which demonstrated marked regression of size and number of lung nodules and additionally increased uptake of ^{18}F-FDG in the region of right tonsil. Head MRI was performed and disclosed a tumor of the base of tongue (size 37×32×35 mm), compressing the tonsil and epiglottis. After ENT consultation and microlaryngoscopy patient was referred to endocrinologist with suspicion of lingual thyroid. The neck ultrasound revealed absence of orthotropic thyroid gland and presence of ectopic thyroid in sublingual region. At the time of diagnosis the patient was hypothyroid with TSH level 21.8 μIU/ml. Autoimmune etiology of hypothyroidism was excluded. Due to compressive symptoms and contraindication for surgery, 22 mCi of 131-radioiodine was administered and L-T_4 replacement therapy have been introduced.
Conclusions
The reported case is exceptional because of advanced age of diagnosis and unusual clinical presentation. Bleeding and hemoptysis, next to local symptoms, dyspnea, dysphagia and dysphonia, can be a manifestation of a lingual thyroid. The described case indicates that PET–CT may provide useful information in diagnostic process of ectopic thyroid gland.

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P327

Hirata disease: a rare form of hyperinsulinemic hypoglycemia

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Introduction
Insulin autoimmune syndrome or Hirata disease is a rare cause of hypoglycemia without prior insulin exposure. Approximately 400 cases were reported, mostly in Japan. It's associated with other autoimmune diseases or exposure to sulfhydryl-containing drugs.

Case report
A 56-year-old Caucasian woman presented with a 20-month history of hypoglycemia ameliorated by sugar intake. She had a past history of autoimmune thyroiditis, asthma and factor XI deficiency. She wasn't taking any medication when evaluated, but had previously taken agomelatine, fluticasone/salmeterol, naproxen, acetylsalicylic acid and lorazepam. 72 h fast was negative. Prolonged 75 g oral glucose tolerance test (OGTT) revealed hypoglycemia after 240 min (39 mg/dl). Peak insulin was 5170 pmol/l (PerkinElmer AutoDELFIA®) at OGTT 120 min, with a recovery of 23% (>70%) after polyethylene glycol precipitation. Anti-insulin antibodies were strongly elevated at 600 U/ml (RiaRSR® IAA, reference <0.4). Gel filtration chromatography demonstrated high-molecular-weight insulin immunoreactivity suggesting the presence of insulin-antibody complexes. HLA typing revealed DRB1*04:04, DRB1*13, DQB1*04:02/DQB*06:03, DQA1*01:03/DQA1*03:01, the first and latter haplotypes being associated with Hirata disease. Patient's clinical status improved after 1 g of methylprednisolone i.v. pulses for 2 days every 4 weeks. Two OGTTs during treatment revealed shorter insulin peaks with faster clearance than pre-treatment, however high titres of insulin autoantibodies were still measured. If clinical improvement resulted from the therapeutic approach or from spontaneous remission, which occurs in up to 80% of the cases, is unclear. Progressively lower insulin peaks during OGTT paralleled with persistently high insulin autoantibody titres may indicate that not all antibodies form insulin-antibody complexes in plasma. This leads to another challenge: how to best monitor disease activity during treatment?
Conclusion
Hirata disease should be considered in any patient with hyperinsulinemic hypoglycemia and positive anti-insulin antibodies. The presence of insulin-antibody complexes can influence the approach to the patient and should be tested. The best follow-up strategy is unknown.

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P328

Gynecomastia: a rare etiology

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Introduction
Gynecomastia is a frequent reason for endocrinology consultation and its correct investigation is pivotal towards a precise diagnosis. We present a clinical case of a rare cause of gynecomastia.
Case report
A 56-year-old male was referred to the hospital setting for an endocrinology consultation. He noticed increased breast size for a year, initially tender to palpation, and unquantified weight loss. Neither galactorrhea, nor any nipple discharges were observed. He reported no decreased libido and no erectile dysfunction. On further history assessment, medication was irrelevant and no nonprescription medications, anabolic steroids and dietary supplements were taken. Past history was negative, except for mumps in his childhood. He had four children, all healthy. On physical examination, body mass index was 26 kg/m^2 and hair distribution was normal, with beard. Breast examination revealed bilateral retroareolar gynecomastia and on testicular examination, both testes were found in the scrotal pouch, with approximate sizes of 20 ml (right) and 12 ml (left). Hormonal assessment demonstrated only a slight elevation of estradiol. Tumour markers were normal. Scrotal ultrasound revealed a hypoechoic, hypervascularized nodule, 3 cm in size, within the right testicle. Patient was referenced for urology consultation, where testicular biopsy was performed, revealing Leydig cell carcinoma. After right orchiectomy, regression of gynecomastia was observed.
Conclusion
This case report illustrates the importance of a complete medical history, with a good physical examination, and an adequate workup management, to avoid underestimation of rarer, but potentially more severe causes of gynecomastia.

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P329

Two serious complications of propylthiouracil treatment in the same patient: case report

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Introduction
Thionamides are important drugs in the treatment of hyperthyroidism. Despite that, they can be associated with rare but serious complications, which require drug discontinuation.
Case report
Sixty-five-year-old woman with Graves' disease, treated in 2002 with methimazole and in remission until 2012. Recurrence of Graves' disease was diagnosed in March 2012 and she was started on propylthiouracil (PTU) 150 mg per day. She presented for the first time to our institution 2 months later, with fever and odynophagia. Severe agranulocytosis (neutrophils 20/ul) with upper respiratory tract infection and oral candidiasis was diagnosed, requiring hospitalization. PTU was stopped and filgrastim (G-CSF), ciprofloxacin, nistatin, prednisolone and bisoprolol were started. Lugol's solution was stopped because she developed a skin rash after the first administration. During hospital stay, she developed a small vessel, pANCA positive, inflammatory vasculopathy, with multiple organ involvement (pulmonary – nonspecific interstitial pneumonia; cutaneous – palpable purpura and ulcerations; hematologic – pancytopenia; glandular – sialadenitis and acute pancreatitis; and splenic – splenic infarct), and was transferred to the Intensive Care Unit. She then began metilprednisolone 1 mg/day during 3 days, maintaining prednisolone 1 mg/kg per day for the next days, with favorable evolution and resolution of organ dysfunctions. She was finally submitted to total thyroidectomy and was discharged (at D51), referenced to a Physical Medicine and Rehabilitation Center.
Conclusion
This case report illustrates two serious complications of thionamide treatment, that requires a high index of suspicion and an adequate monitoring. These diagnoses require thionamide discontinuation and establishment of a definitive treatment.

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P330

Brain metastatic disease in a patient with tall cell thyroid carcinoma

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Papillary thyroid carcinoma is a disease associated with a very good prognosis. However, there are some subtypes of papillary thyroid cancer which are associated with aggressive biological behavior and worse outcome. The appearance of brain metastatic disease in the course of papillary thyroid carcinoma is rare and carries an unfavorable prognosis.
The aim was to describe the case of a patient with tall cell papillary thyroid carcinoma who presented with brain metastatic disease.
A patient, male, aged 63 years, presented with a large mass in the area of the thyroid causing dysphagia. Initial evaluation with thyroid hormone measurement and a fine needle aspiration biopsy revealed the presence of malignancy. Near total thyroidectomy was performed. On histology a large tumor measuring 7.0×7.0×5.0 cm and weighing 122 g was examined. The tumor was multi-lobular, scleroelastic and had a small area of fibrosis and an area of cystic degeneration. The neoplasm was a tall cell papillary thyroid carcinoma which had foci of dedifferentiation. Within the area of low differentiation atypical mitoses were observed with a Ki67 index of approximately 10%. The tumor was positive to p53 in 50% of the cells. Extrathyroidal extension was observed. After near total thyroidectomy therapeutic radiodine was administered. Approximately a year later the patient presented with brain metastases.
Brain metastatic disease from thyroid cancer is rare and carries a bad prognosis. Some subtypes of papillary thyroid cancer, such as the tall cell variant have an increased propensity to develop metastatic disease, including brain metastatic disease. In conclusion, the case of a patient with a tall cell thyroid carcinoma with areas of low differentiation is presented who developed early brain metastatic disease.

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P331

Thyroid papillary microcarcinoma presenting as parotid metastasis: a case report

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Differentiated thyroid carcinoma is the most common endocrine malignant tumor. Papillary carcinoma frequency in our country is 80% of thyroid neoplasia. Papillary thyroid carcinoma usually metastasizes to cervical lymph. Metastases to distant organs are rare and most often affect the lungs, liver and bones. Despite of its anatomical proximity, metastasis parotid have not been described in the existing papillary carcinomas literature. We report a case of parotid gland metastasis as the first manifestation of an occult papillary microcarcinoma.
A 30 year old male is derived to maxillofacial surgery because of the appearance of a painless tumor at the right parotid level. An ultrasound report reveals a right parotid increased in size, with a lesion in its hypoechoic interior, with lobulated margins that measure 23×22×27 mm. With these data, he is intervened, being the parotid tumor resected. Pathologic diagnosis of serous salivary gland (parotid) with papillary adenocarcinoma infiltrating intraparotid lymph nodes and does not affect resection margins. The patient is sent to endocrinology consultation for further study. Exploration of the thyroid is normal showing no nodules or lymphadenopathy. Thyroid ultrasound shows normal size of right and left lobe. A left lobe level there is a well defined solid nodule, hypoechoic of 4×6×6 mm. A cytology by FNA result suggestive of papillary carcinoma. A complete thyroidectomy with central and bilateral lymph node dissection was performed. The pathological report is: Right lobe without alterations. Left lobe with two focus of papillary carcinoma of 0.4 and 0.1 cm which do not infiltrate the capsule. We present the first case of parotid metastasis from an occult thyroid microcarcinoma.

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P332

Medullary and papillary thyroid cancer metastasis in the same lymph node: case report

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Introduction
Two tumors originating from different cells in the thyroid to metastasis same lymph nodes is very rare. We aimed to present that the same lymph node metastasis of medullary and papillary thyroid in a case.
Case
A 4-year-old male presented with backache without a formerly known disease, has no other property in the patient's history. Vertebra BT was taken and T_2, T_4, T_6 vertebral metastasis have been detected. Malignant cytology was seen in the biopsy from T_4 vertebrae. Thyroid ultrasound was performed to determine primary tumor foci. Malignant nodule (10×23×23 mm) in the left lobe of the thyroid gland and bilateral multiple pathological lymph nodes in the neck were shown. Fine needle aspiration (FNA) biopsy of the thyroid has been reported as malign. Also medullary thyroid cancer (MTC) was thought because of the height of CEA and calcitonin (Calcitonin >2000 pg/ml, CEA 538.3 ng/ml). Malignant involvement was detected in the left lobe of the thyroid gland and increased FDG uptake was determined in the cervical, mediastinal, hilar, abdominal lymph nodes and multiple bones using PET–CT. The patient underwent total thyroidectomy and neck dissection. Multifocal papillary thyroid carcinoma (PTC) in the right lobe, multifocal MTC in the left lobe and isthmus, MTC metastasis in the multiple lymph nodes, PTC and MTC metastasis association in the central area were reported as a result of pathologic. The patient underwent with external radiotherapy for bone metastases. Then systemic chemotherapy and sorafenib was given by medical oncology.
Conclusion
The MTC originating from parafollicular C cells of the thyroid and PTC originating from follicular cells of the thyroid to metastasis to same lymph nodes is very rare. This situation can be explained by the activation of a common tumorigenic pathway for both follicular and parafollicular cells or coincidental.

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Developmental Endocrinology

P333

Effect of glycemia on sleep indicators for patients with type 1 diabetes mellitus

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Study evaluates the impact of glycemia on the parameters of night's sleep for patients with decompensated type 1 diabetes mellitus (T1DM).
Materials and methods
A total of 21 cases with T1DM (HbA1c 8.5%). The monitoring of the average daily glycemia was performed through 'SGMSGold Medtronik' (USA) with estimation of average level of glucose (ALG). Patients divided into groups: group A – 10 patients with ALG ≤7.75 (6.5–8.3) mmol/l, group B – 11 patients with ALG 11.6 (8.9–16.6) mmol/l. All patients underwent polysomnographic monitoring by diagnostic complex 'SOMNOlab2'.

Comparative results ($P<0.05$).

Indicators	Group A	Group B
ALG (mmol/l)	7.75 (6.5–8.3)	11.6 (8.9–16.6)
Duration of hyperglycemia/day (%)	16.5 (6.0–34.0)	68 (21–86)
Duration of normoglycemia/day (%)	80 (61–92)	32 (14–79)
Sleep onset latency (SOL; min)	56.5 (20–133)	14 (12–80)
Efficiency of sleep phase3 (%)	45.6 (30.5–74.8)	35.8 (15.9–50.9)

Results
The analysis revealed a significant correlation between ALG and SOL ($r=0.71$); the duration of hyperglycemia during a day (%) and latency of REM-sleep phase ($r=0.76$); negative correlation between the duration of euglycemia during the day before sleep study (%) and the latency of REM-sleep phase ($r=-0.79$); between HbA1c Sleep latency and ($r=-0.89$) in group A. There was no correlations between factors listed above, but a correlation between ALG and total sleep time ($r=0.83$), efficiency of sleep phase1 ($r=0.85$) and efficiency of sleep phase 2 ($r=0.85$; all $P<0.05$) in group B.
Conclusions
ALG affects on dates of the upcoming night sleep in decompensated T1DM patients. ALG >8.3 mmol/l increases total sleep time, the efficiency of sleep phase 1 and 2. The increasing of ALG extends SOL, latency of REM-sleep phase. Duration of euglycemia during the day reduces latency of REM-sleep phase.

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Physiological expression of thyroid hormone receptors during zebrafish development and effects of their molecular disruption

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Thyroid hormone action defects (THADs) are caused by the defective action of thyroid hormones (THs) through their receptors (TRs). TRs variants (TRα1 or TRβ) are associated with several defects, which depend mainly on the tissue-specific expression of the defective-receptor. One of the most striking manifestations is the deregulation of the hypothalamus–pituitary–thyroid axis (HPT); patients with TRα1-mutations show normal thyroid volume, low T4/T3 and high T3/rT3 ratios. Conversely, patients carrying TRβ-mutations exhibit goitre, high T4 and T3 production with unsuppressed TSH. In this study we take advantage of the zebrafish model to further understand the role TRs during development and in the HPT axis regulation. The tissue-specific expression of TRs are analysed by RQ-PCR and whole mount *in situ* hybridization at several developmental-stages. We than create two different mutant-lines (MOs_TRα1 and MOs_TRβ) using specific morpholinos, and we studied the of the HPT axis by several techniques. In zebrafish the expression of TRs is temporally and tissue-specific regulated. During the embryonic development, TRs are expressed during the first 4 h-post-fertilization (hpf), followed by a down-regulation window until 24 hpf, when the expression is again up-regulated in tissue-specific manner: TRα1 is prevalently expressed in brain, heart, thyroid, and gastrointestinal tract; TRβ is prevalently expressed in the pituitary, eyes and otic vesicles. The generation of different 'heterozygous-like' mutant-lines by specific antisense-RNAs shows that

MOs_TRα1 exhibit low thyroid volume, low TSHβ and T4 production but high T3 content. Conversely, MOs_TRβ present high thyroid volume, high T4 and T3 content but unsuppressed TSHβ. In conclusion, the TRs are expressed in a temporal and tissue-specific manner revealing novel insights on TH-dependent developmental effects. The TR-mutants recapitulate the HTP axis alterations found in patients with the two forms of THADs, representing a new useful biotool to test human TRα and TRβ variants.

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P335

Clinical and molecular profile of patients with gonadal dysgenesis attending tertiary care hospital.

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Introduction
Gonadal dysgenesis (GD) is a congenital disorder which results in defective development of gonads. GD may be due to mutation(s) in any of the genes involved in gonadal development and differentiation. Here we present clinical and molecular profile (SRY and SOX9 gene) of patients with GD at our hospital.
Methodology
Detailed clinical examination, karyotyping and molecular analysis of patients was done for *SRY* and *SOX9 gene.* The work has been approved by Institute Ethics Committee. A written informed consent was taken from all patients.
Results
We had 11 patients (2011–2013) diagnosed with GD. The present age of the patients was 19.0±9.0 years. The age at presentation was 14.8±8.5 years. Cytogenetic studies revealed 46, XY in 9 patients, 46, XX in 1 patient and 45, XO/46, XY in 1 patient. Ultrasonography for localization of gonads was done in eight patients. Four patients had dysgenetic gonad on one side with contralateral streak gonad on the other side, three patients had bilateral dysgenetic gonads and two had bilateral undescended testis. Molecular analysis revealed normal sequence of *SRY* gene, while as in *SOX9* gene a transition of G>T at position 1776 (rs2229989) was found in 6 patients which was absent in controls.
Conclusion
The patients with gonadal dysgenesis need detailed molecular evaluation of all the genes involved in gonadal differentiation pathway. Also the base transition at position 1776 of *SOX9* gene may alter the tertiary structure of protein.

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P336

Cord blood insulin-like peptide 3 (INSL3) but not testosterone is reduced in idiopathic cryptorchidism

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Background
Cryptorchidism, the most frequent congenital malformation in full-term male newborns increases risk of hypofertility and testicular cancer. Most cases remain idiopathic but epidemiological and experimental studies have suggested the role of both genetic and environmental factors.
Objectives
To study in isolated cryptorchidism, two major leydig cell hormonal actors of testicular descent, insulin-like peptide 3 (INSL3) and testosterone at birth.
Methods
From a prospective case-control study at Nice University Hospital, we assessed 180 boys born after 34 weeks gestation: 52 cryptorchid (48 unilateral, 4 bilateral; 26 transient, 26 persistent), and 128 controls matched for term, weight and time of birth. INSL3 and testosterone were measured in cord blood and compared in both groups.
Results
INSL3 was decreased in cryptorchid boys ($P=0.031$), especially transient cryptorchid ($P=0.029$), while testosterone was unchanged**.** In the whole population, INSL3 correlated positively with LH and negatively with AMH, but with no other measured hormones.
Conclusions
INSL3 but not testosterone is decreased at birth in idiopathic cryptorchidism especially in transient forms. Since *INSL3* gene expression is negatively regulated by estrogens, fetal environment (nutrition, endocrine disruptors) may interfere through impairment of *INSL3* in idiopathic cryptorchidism, along with genetic and non genetic components.

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P337

Crystal structure of *Drosophila* imaginal morphogenesis protein-Late 2 (IMP-L2) in free form and bound to *Drosophila* insulin-like peptide 5 (DILP5) and human Insulin-like growth factor-I (hIGF1).

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The insulin signalling system including the insulin receptor tyrosine kinase (IRTK) is evolutionarily ancient. The *Drosophila Melanogaster* genome contains seven genes for insulin-like peptides (ILPs) that are expressed in neurosecretory cells in a highly tissue- and stage-specific pattern, DILP1–7. There is however only one IRTK (dIR). This system is important in the regulation of metabolism, growth, reproduction and lifespan. We reported in 2011 the crystal structure of Drosophila insulin-like peptide 5 (DILP5) (expressed in *Saccharomyces Cerevisiae*) at 1.85 A resolution, as well as its biological and receptor binding properties. DILP5 shares the canonical fold of the insulin peptide family and form dimers that differ from the mammalian and hagfish insulin dimers.
Drosophila Melanogaster also has a circulating ILP binding protein, called imaginal morphogenesis protein-Late 2 (IMP-L2), with no equivalent in mammals. It was cloned, expressed and purified in 2000 and was shown to bind human insulin and insulin-like growth factors. We showed in 2011 that it also binds DILP5. We now report the solution of the crystal structure of IMP-L2 in the free form as well as bound to DILP5 and to human insulin-like growth factor-I (hIGF1). Recombinant IMP-L2 was expressed in a Baculovirus expression system, purified and crystallized with selenium as heavy atom. IMP-L2 shows a bilobed structure with two IgG beta sheet modules folded together into a 'baseball glove'. The structure is very different from the known partial structures of IGFBPs and dispels the concept that IMPL-2 is an orthologue of a human IGFBP. The complex of IMP-L2 with DILP5 shows a multimeric structure with two DILP5 molecules bound into the grooves between the beta sheets of two distinct IMP-L2s in a symmetrical tetrameric IMPL-2. In contrast, the IMPL-2 complex with hIGF-I is monomeric and reveals a novel conformation of IGF1 not seen in previous structures of IGF1.

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P338

Genome-wide survey for clinically relevant structural abnormalities contributing to pathogenesis of combined pituitary hormone deficiency (CPHD) with childhood onset.

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Introduction
Combined pituitary hormone deficiency (CPHD) results in deficit of growth hormone and coexisting failure of synthesis or excretion at least another pituitary hormone. Transcription factors controlling expression of genes required for pituitary organogenesis are orchestrating entire development process and certain cell lineages differentiation, contributing therefore significantly to CPHD pathogenesis with childhood onset.
Aims
The purpose of the study was a genome-wide screening using microarrays for novel factors controlling pituitary organogenesis (genes, CNV), and contributing to combined pituitary hormone deficiency (CPHD).
Methods
The entire CPHD cohort of patients consist of 102 individuals. All patients were screened for mutations and copy number of known pituitary related genes (*PROP1*, *POU1F1*, *HESX1*, *LHX3* and *LHX4*) using sequencing and MLPA. Fifty-six patients without identified alterations were screened for genomic imbalances employing microarray technology (Illumina, Affymetrix). Genomic size of CNVs, their location, clinical significance and encompassing genes were thoroughly examined. Parental studies were conducted to determine pathogenic CNVs and the inheritance in a subset of cases where parental samples were referred for follow-up testing.
Results
Among genomic changes we identified recurrence of deletions and duplications. Further examination revealed presence of genes playing a role in pituitary functioning (i.e. PPYR1) or transcriptional regulators (ZNF826, ZNF737). A cohort of CNVs shows overlap with clinically valid regions deposited in DECIPHER and ClinVar databases, and reporting complex clinical phenotypes including growth abnormalities.
Conclusions
Given the rapid expansion of efficient genomic technologies, examination of substantial group of CPHD patients will result in emerging novel interesting targets and determine significance of recurrent rare CNVs. This data will facilitate our understanding of complexity of pituitary processes and hopefully will support diagnosis, management, and care CPHD patients in the future.

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P339

Influence of growth hormone therapeutic supplementation on early hematopoietic stem/progenitor cells in patients with growth hormone deficiency (GHD).

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Objectives
GH plays a crucial role in the regulation of metabolism of human cells. Nevertheless, a direct influence of this hormone on the proliferation, maturation and differentiation of human early hematopoietic stem/progenitor cells (HSPCs) has not been investigated thoroughly. Moreover, certain deviations of hematological parameters, such as anemia or leucopenia, are commonly observed in patients with growth hormone deficiency (GHD) syndrome, which might be substantially compensated during the therapeutic GH supplementation. However, the mechanisms of GH cellular action and interactions with HSPCs from these patients are not well known. We explored whether the possible impairment of GH-mediated regulatory mechanisms in human hematopoiesis has any direct influence on proliferation/differentiation of HSPCs collected from patients with GHD, who underwent the exogenous GH supplementation therapy.
Materials and methods
Blood-derived $CD34^+$-enriched HSPCs were isolated from GHD patients at the time of diagnosis, and subsequently in the 3rd and 6th month of the scheduled regular GH therapy. Healthy volunteers served as controls. The expression of the growth hormone receptor (GHR) on HSPCs was examined by flow cytometry and immunocytofluorescence. Next, the growth of granulocyte–macrophage colony-forming units (CFU-GM), erythrocyte burst-forming units (BFU-E) and lymphocyte colony-forming units (CFU-L) was determined in clonogeneic *in vitro* assays. Additionally, the gene expression of the cell-cycle regulatory molecule, such as proliferating cell nuclear antigen (PCNA) was examined by qRT-PCR.
Results
GHR expression was detected at the protein level in the population of human early HSPCs. GHD patients displayed decreased clonogeneic potential of BFU-E, GM-CFU and CFU-L, which was significantly increased after prolonged GH therapeutic supplementation. Similarly, GH supplementation activated the molecular response of HSPCs through an increase in *PCNA* gene expression in the analyzed cells.
Conclusions
We have shown that GH may directly play a significant role in the regulation of growth and differentiation of human early hematopoietic stem/progenitor cells.

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Diabetes (epidemiology, pathophysiology)

P340

Metformin may reduce bladder cancer risk in patients with type 2 diabetes

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Background
Whether metformin therapy affects bladder cancer risk in patients with type 2 diabetes mellitus (T2DM) has not been extensively investigated.
Methods
The reimbursement databases of all Taiwanese patients with a new diagnosis of T2DM between 1998 and 2002 ($n=940708$) were retrieved from the National Health Insurance for follow-up of bladder cancer up to the end of 2009. Of these patients, 532519 were never-users and 408189 were ever-users of metformin. A time-dependent approach was applied in the calculation of bladder cancer incidence and in the estimation of hazard ratios by Cox regression.
Results
During the study period, 1874 (0.45%) metformin ever-users and 6213 (1.17%) metformin never-users developed bladder cancer, representing an incidence of 72.03 and 189.22 per 100,000 person-years respectively. The age-sex-adjusted and multivariable-adjusted hazard ratios (95% confidence intervals) for ever- vs never-users were 0.335 (0.256–0.437) and 0.600 (0.564–0.638) respectively. The multivariable-adjusted hazard ratios for the first, second, and third tertiles of cumulative duration of metformin therapy were 1.034 (0.954–1.120), 0.696 (0.632–0.766) and 0.258 (0.229–0.291) respectively (P-trend <0.0001) were 0.997 (0.920–1.080), 0.615 (0.559–0.677) and 0.285 (0.253–0.321) respectively (P-trend <0.0001) cumulative dose of metformin.
Conclusions
Metformin use is associated with a decreased risk of bladder cancer.

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P341

Exenatide protects pancreatic islets against brain death-induced inflammation and viability loss

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Introduction
Pancreatic islet transplantation is an attractive approach to re-establish glycemic homeostasis in patients with brittle type 1 diabetes. However, islet damage along the isolation procedure limits the availability of viable islets for transplantation.

The donor's brain death (BD) is among the factors contributing for islet quality loss in this scenario. Exenatide, a glucagon-like peptide-1 (GLP1) analog, exerts anti-inflammatory effects leading to an increase in islet cell viability *in vitro*. Here, we hypothesize that this drug could alleviate the damage caused by BD on pancreatic islets, thus improving the quality of such islets for transplantation. We proposed a study in a murine model of BD in which the administration of Exenatide was evaluated in respect to islet quality parameters.
Methods
Animals were separated into three groups: Sham, BD, and BD plus Exenatide 5 μg/kg (EXE). Islet viability was determined by FDA/PI assay, and gene expressions of *IL-1β* and *Bcl-2* were assessed by RT-qPCR.
Results
A striking viability reduction was observed in islets isolated from the BD group *vs* sham and EXE groups (59.8±15.5% vs 88.6±4.8 vs 91.6±0.6; $P=0.011$). Furthermore, a robust and significant increase in *IL-1β* gene expression was seen in the pancreatic tissue of animals from BD group (17.5±12.1 vs 1.9±1.7 vs 1.9±2.6 arbitrary units (AU), $P=0.012$). Our data also suggest a greater expression of *Bcl-2* in islets originated from the BD group (1.36±0.12 vs 1.0±0.25 vs 0.93±0.28 AU; $P=0.11$). Although this difference was not formally statistic, it suggests a compensatory effect to counteract the excessive cell death induction in islets originated from the BD group.
Conclusion
Our data indicate an increase in the inflammatory state as well as a reduction in the cell viability of islets isolated from the BD group. Exenatide administration following the establishment of the BD seems to protect the islets against such deleterious effects.

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Higher HDL cholesterol to apolipoprotein A-I ratio is protective against the development of type 2 diabetes

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Aims
HDL have many diverse functions. The goal of this study was to determine the differential effect of HDL cholesterol (HDL-C) and apolipoprotein A-I (apoA-I) on the development of type 2 diabetes (T2D). In addition, this study determined the association between the ratio of HDL-C to apoA-I (HA) and incident T2D.
Methods
A total of 27 988 subjects with impaired fasting glucose (IFG) (18 266 men and 9722 women) aged 21 to 91 years (mean age 43.5 years) were followed for a mean duration of 2.81 years.
Results
The study subjects were divided into four groups according to median HDL-C or apoA-I concentrations: lower HDL-C and upper apoA-I (LU group), lower HDL-C and apoA-I (LL group), upper HDL-C and apoA-I (UU group), and upper HDL-C and lower apoA-I (UL group). The LU group had the least favorable metabolic profile and the UL group had the most favorable metabolic profile. The LU group was associated with the highest incidence of T2D independently of other risk factors for T2D and serum triglyceride concentrations, while the UL group had the lowest incidence of T2D. In addition, incident cases of T2D decreased as the HA ratio increased independently of other risk factors for T2D and serum triglyceride concentrations.
Conclusion
High HDL-C combined with low apoA-I was associated with a low incidence of T2D in patients with IFG. However, the protective effect of HDL-C lessened as apoA-I increased.

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Relationship between age and Hba1c in Turkish patients

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Hemoglobin A1c (HbA1c) has been used as a clinically significant evaluation tool for analyses regarding glycemic control. Guidelines recommend patients with type 2 diabetes mellitus (T2DM) should aim for an A1C≤7.0%, but real world data is limited in the elderly regarding outcomes associated with different A1C levels.
A thousand six hundred Turkish cases were enrolled in this study. The mean age of the patients was 57 (17 to 91) years. The mean HbA1c value of the cases was 8.05±2.28. The mean HbA1c values were 8.23±2.4 for males ($n=583$) and 7.94±2.2 for females ($n=1017$). This difference was statistically significant ($P=0.013$). HbA1c value was below targeted value (7%) in 43% of the cases.
The mean HbA1c values were 6.19±0.45 for the patients with HbA1c <7 ($n=693$) and 9.46±2.09 for the cases HbA1c >7 ($n=907$). A strong positive correlation was detected between age and HbA1c ($P<0.001$, $r=0.089$).
The mean age was 55.9±13.78 in the patients with <7 HbA1c value and it was 58.39±11.4 in the cases with >7 HbA1c. This difference was significant ($P<0.001$).
The mean HbA1c values were 8.04±2.33 for the patients below 65 and 8.07±2.16 for geriatric cases. There is no statistically significant difference between geriatric patients and the cases below 65 ($P>0.05$).
The strong correlation between age and HbA1c may be of the increase of comorbid disorders, reduced hospital application in older age and decrease of therapeutic compliance. This hypothesis should be needed validation through randomized controlled trials.

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P344

Features and outcome of stroke related to type 2 diabetes mellitus (T2DM) in a community hospital

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Introduction
Population with DM are at substantially increased risk for stroke. Someone who's had diabetes less than 5 years has a 70 percent increased risk of ischemic stroke, for 5–10 years has an 80 percent increased risk compared to someone without diabetes. Duration longer than 10 years was linked to more than a threefold increase in the risk.
Methods and patients
We study all patients admitted at internal medicine department with diagnosis of stroke and T2 DM, during the last 3 years. We analyse, age, gender, comorbidities, laboratory test, radiology, treatment and outcome.
Results
Of 338 patients admitted for stroke 97 (28.69%) had DM, 51 men and 46 women of 78.17±9.5 years-old. Duration of DM 10.6±4.9 years (range 2–40). The 47% had a length of 10 years or more. Comorbidities, hypertension 82%, dislipemia 47%, atrial fibrillation 26%, previous strokes 23%, IHD 19%, chronic renal disease 19%, obesity 18%, peripheral arteriophaty 16%, cognitive impairment 14%, smoker 13%, retinopathy 12%. Laboratory test: HbA1c 7±1.2%(5.3–10), cholesterol 163.3±43.42 mg/dl, HDL 46±16.5 mg/dl LDL 124±67 mg/dl, TG 124±67 mg/dl. Radiology; CT/MRI disclose, ischemic lesion in 90% (hemispheric, lacunar infarction and TIA), haemorrhage in 10% and in 82% disclose chronic vascular lesions. Carotid US showed ateromatosis in 64%.treatment. Metformin 48%, insulin 28%, sulphonilureas 21%, other (DPP4, glinides, glitazones,) 17%, only diet 5%. Monotherapy 67%, dual therapy 28%, triple therapy 5%. Treatment for cardiovascular risk factors: IECAS/ARAB 41%, statins 39%, antiplatelet 26%. Outcome. Discharge with sequels 29%, a new stroke appeared in 7 patients during follow-up. In-hospital mortality 8%.
Conclusions
Duration of DM up of 10 years in 47%. Hypertension was main cardiovascular risk factor adequate control of cardiovascular risk factors and glycated haemoglobin. Low mortality but high disability. Metformin was more used drug, monotherapy was main therapeutic regimen.

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P345

CTRP3 increased the insulin sensitivity of 3T3-L1 adipocyte via decreasing the expression of inflammation factors

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Objective
To investigate the effects of C1q/TNF related protein 3 CTRP3 on the insulin sensitivity of adipocyte and its possible mechanisms.
Methods
The insulin resistance model of 3T3-L1 adipocyte was induced by palmic acid (PA) cultivation. Such adipocytes were treated with different concentration of recombinant CTRP3 (0,10,50,250,1250 ng/ml) for 12 h, and for different time (2, 6, 12, 24 h) at the concentration of 250 ng/ml. The glucose consumption was detected by glucose oxidase method. The glucose transport ratio was inspected by 2-deoxidation-H^3-glucose intake method. The contents of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) in supernatant were detected by enzyme-linked immunosorbent assay (ELISA). The relative expression of TNF-α, IL-6 and glucose transporter-1 (GLUT-4) were measured by fluorescence RT-PCR.
Results
With the increased concentration of CTRP3 (10,50,250,1250 ng/ml), the glucose consumption were increased by 22.1, 42.9, 76.6, and 80.5% respectively (all $P<0.01$), the glucose intake ratio were increased by 39, 68, 108, and 111% respectively (all $P<0.01$) in compared with that in control group which were not treated with CTRP3. With the increased duration (2, 6, 12, 24 h) of CTRP3 treatment at the concentration of 250 ng/ml, the glucose intake ratio were increased by 23, 79, 109, and 114 respectively (all $P<0.01$). The contents of TNF-α and IL-6 in supernatant were decreased by 17.4 and 17.1% respectively (all $P<0.01$) as treated with CTRP3 at the concentration of 250 ng/ml for 12 h, and the relative expression of TNF-α and IL-6 mRNA were decreased by 26 and 19% respectively (all $P<0.01$), while the relative expression of GLUT-4 mRNA was increased by 62% ($P<0.01$).
Conclusion
CTPR3 may increase the insulin sensitivity of adipose tissue though the decreased expression of inflammation factors, improved insulin signal transduction and increased the expression of GLUT-4.
Keywords
CTRP3, 3T3-L1 adipocyte, insulin resistance, inflammation
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P346

Thyroid autoimmunity in children and adolescents with type 1 diabetes mellitus

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Background
The purpose of this study was to investigate the occurrence of autoimmune thyroid disease in children and adolescents at onset of type 1 diabetes mellitus (T1DM) and to assess whether the presence of diabetes-specific autoantibodies may predict the autoimmune thyroid disorder.
Methods
Seventy-three children with T1DM were recruited in the study. Glutamic acid decarboxylase antibodies (GADA), Islet cell antibodies (ICA), insulin autoantibodies (IAA), and thyroid antibodies were determined for all patients at the time of diagnosis.
Results
The majority of patients (87.7%) had at least one pancreatic antibody (74.0% for GADA, 20.5% for ICA, and 24.7% for IAA). Thyroid autoantibodies were found in 19 of 73 patients (26.0%) at diagnosis. Thyroid autoimmunity (TA) incidence was not statistically significant by GADA or ICA positivity, but significantly high by IAA positivity ($P=0.03$) and IAA positivity showed 4.5 odds ratio (95% CI) for TA ($P=0.008$).
Conclusions
The IAA positivity in children and adolescents with TIDM was found to be strongly related to the positivity of thyroid autoantibodies and thus it could serve as an index for the early prediction of the development of the thyroid autoimmune disorder among children and adolescents with TIDM.
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Risk of diabetes mellitus after first-attack acute pancreatitis: a national population-based study

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Objective
We longitudinally assessed the overall and age- and sex-specific incidence rates and relative risks of newly diagnosed diabetes mellitus in patients surviving the first-attack acute pancreatitis (AP) as compared to matched controls.
Methods
Study cohort included 2966 AP patients and 11 864 non-AP controls individually matched on age, sex and date of index admission, with an AP/non-AP ratio of 1:4. Incidence rate was estimated under Poisson assumption; and relative risks of diabetes were indicated by hazard ratio estimated from Cox proportional hazard regression models.
Results
The incidence of diabetes was 49.7 and 21.1 per 1000 person-years for AP and control groups, respectively; representing a covariate-adjusted hazard ratio (HR) of 2.06 (95% CI 1.85–2.30). The risk of diabetes was greater in men than in women (HR 2.46 vs 1.42) and in patients with severe AP than in those with mild AP (HR 2.40 vs 1.99). In men, the risk was the most increased in young adults aged <45 years with severe AP (HR 5.29), whereas in women, the effect of age was less obvious. For older people ($\geqq 65$ years), the risk was non-significant, regardless of sex and AP severity. Moreover, mild AP was also significantly associated with increased risk of developing insulin-dependent diabetes (HR 5.05, 95% CI 1.75–14.55). The exclusion of patients with subsequent recurrence of AP only slightly reduced the HRs, but did not change the results.
Conclusions
The risk of diabetes doubles after AP, indicating a need of long-term screening for diabetes after the first attack regardless of the severity. Future research is needed to further define high risk patients, to find the most cost-effective follow-up strategy, and to elucidate the underlying mechanisms of the relation.
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P348

Low rates of attaining LDL goals despite statin use in diabetic patients in a tertiary healthcare center.

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Introduction
Diabetes and dyslipidemia are two common comorbid conditions encountered in clinical practice. Diabetes is considered as a cardiovascular disease (CVD) equivalent. Most professional organizations suggest statin therapy for diabetic patients, regardless of baseline lipid levels for patients with overt cardiovascular disease or without CVD over 40 years and have one or more other CVD risk factors. For lower risk patients;the LDL goal is 100 mg/dl and for patients with overt CVD the LDL goal is 70 mg/dl.
Materials and methods
In this retrospective review, we aimed to evaluate the statin use of our diabetic patients in a tertiary care endocrinology outpatient clinic.
Results
Total of 136 diabetic patients were evaluated. In the overall group the ratio of statin users was 39.7% ($n=54$), and non-users was 60.3% ($n=82$).
From the total of 136 diabetic patients only 36.8% ($n=50$) patients had an LDL level <100 mg/dl, the remaining 63.2% ($n=86$) patients had an LDL level >100 mg/dl. When cardiovascular disease has been taken into consideration; in the overall group 18.4% ($n=25$) patients had overt cardiovascular disease. Of these 25 patients 68% ($n=17$) was on statin treatment and 32% ($n=8$) was not. Only one (4%) of overt CVD patients reached the LDL goal of <70 mg/dl, and the remaining 24 (96%) had LDL level of >70 mg/dl.
Conclusions
Diabetes is a cardiovascular disease equivalent and statin treatment is required for most diabetic patients for primary or secondary prevention. Our results show that even most overt CVD patients are not on statin treatment and statin treated patients are not on goal. For lower risk patients the number of statin non-users and LDL levels above target is even higher. The reasons for this situation must be carefully addressed and treated accordingly. Further studies are needed to clarify this issue.
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P349

Profile of type 2 diabetic patients according to HbA1c tertiles in our tertiary health care center

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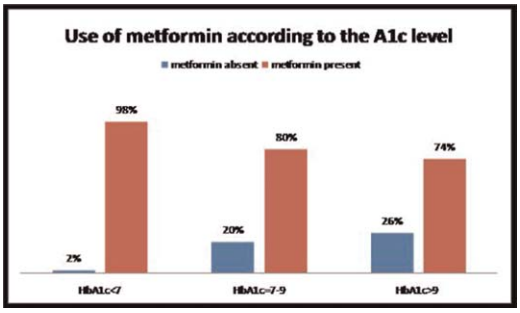
Aim
In this study we aimed to investigate general properties and treatment modalities of our type 2 diabetic patients.
Materials and methods
A total of 136 consecutive type 2 diabetic patients were investigated. Type 2 diabetic patients were divided into three different groups according to HbA1c level (<7% group 1, 7–9% group 2, >9% group 3).
Results
Mean age of our type 2 diabetic patients (F $n=95$, M $n=41$) was 54 years. A1c level of 68% of patients was above 7%. Mean duration of diabetes was 89, 135, and 127 months in group 1,2,3 respectively. Systolic and diastolic blood pressure values were not different significantly. Triglyceride (TG) level was lower in group 1 ($P<0.001$). HDL level was higher in group 1 when compared to group 3 ($P=0.011$). CRP was higher in group 3 compared to group 1 ($P=0.004$). Twenty-six percent of our patients were not using metformin. According to the subgroups, 26% of group 3, 20% of group 2 and 2% of group 1 were not taking metformin ($P=0.009$) (Fig. 1). Four percent of our type 2 diabetic patients were only on diet treatment. While 53% of them were taking oral antidiabetic (OAD) medication, 43% were on insulin treatment. Percentage of thiazolidinedione use was 15%, DPP-4 inhibitor usage was 20%. Vascular complication rate was higher in group 3 ($P=0.019$).
Conclusion
Our low percentage of target A1c level could be due to diabetic patients with new onset and relatively short duration of diabetes. As A1c level increases, percentage of vascular complication increases. Relatively high percentage of metformin nonuser in group 3 is quiet remarkable finding. At this point, drug side effect, compliance, and physician related factors should be re-evaluated.



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P350

Clinical case of type 1 diabetes mellitus and multiple sclerosis – just bad luck?

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Introduction
Type 1 diabetes mellitus (T1DM) and multiple sclerosis (MS) are organ-specific autoimmune diseases. Their association, first described in a study in Sardinia, left questions about their clustering, clarified by the Familial Autoimmune and Diabetes Study, which showed for the first time an highly increased prevalence of MS in adults with T1DM, reinforced by further epidemiological studies that also revealed increased risk of T1DM in MS patients.
Clinical case
A caucasian male, 29 years, was diagnosed with T1DM, after an inaugural ketoacidosis episode. He had no family history of diabetes or neurological diseases. Blood tests: normal thyroid function, ACTH, cortisol, lipid levels; HbA1c 11.7%; C-peptid 0.38 ng/ml (0.8–3.9); 27.5 mg microalbuminuria/24h; positive glutamic acid decarboxylase 2 autoantibodies. He had no diabetic retinopathy or other visual changes. After discharge he kept good clinic and analitical control; his HbA1c reduced to 5.7% in four months. Suddenly, he started complaining about intermittent floating paresthesias in limbs' extremities, without hypoesthesia, burning sensation, muscle weakness, or other symptoms. B12 vitamin, folic acid levels were normal; celiac disease antibodies negative. Monofilament test, electromyography, and nerve conduction study were normal. As symptoms persisted, he was refered to a neurologista. Brain MRI showed multiple infracentimetric lesions, suggesting primary demyelinating disease. He was diagnosed with MS.
Conclusions
T1DM and MS are autoimmune inflammatory diseases affecting respectively pancreatic β-cells or myelin sheath in central nervous system.
Pathophysiology underlying this co-occurrence remains unclear, although envolves T-cell mediated imune abnormalities. HLA haplotypes were considered mutually exclusive for MS and T1DM, but autoimune diseases' genetic susceptibility envolves several genes.
This patient was diagnosed with MS one year after being diagnosed with T1DM, which may suggest simultaneous activation of autoimmune pathways.
The mechanism explaining the association between these two diseases still needs further clarification, leading to improvement in prevention and therapy.

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P351

A rare presentation of type 2 diabetes: diabetic ketoacidosis, acute pancreatitis, and hypertriglyceridaemia

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Introduction
The triad of diabetic ketoacidosis (DKA), acute pancreatitis (AP), and hypertriglyceridaemia (HTG) has been described mainly in T1DM with few cases in T2DM. We report the first case of this triad revealing T2DM.
Case report
A 30-year-old male with strong family history of T2DM presented to the emergency with severe epigastric pain radiating to the back associated with abdominal swelling, vomiting and diarrhea. He also reported history of polyuria and polydipsia with undocumented weight loss for one month prior to presentation. Clinically, he was found to have distended abdomen which was tender all over especially in the epigastrium. A urine dipstick was positive for +3 ketone and +3 glucose. The serum glucose level was 30.6 mmol/l. Blood work demonstrated high anion gap metabolic acidosis, high amylase and moderate hypertriglyceridaemia (10.67 mmol/l). A CT scan of the abdomen revealed that the pancreas was bulky with peri-pancreatic fluid collection suggestive of acute mild exudative pancreatitis. The diagnosis of DKA, AP precipitated by HTG was established. The patient was managed with intravenous fluid, potassium replacement, and insulin infusion in addition to analgesic until he improved. He was then shifted to multiple doses of insulin and started on fenofibrate 145 mg daily. The C-peptide was 538 pmol/l (366–1466). The HbA1c was 10%, and all pancreatic auto-antibodies were negative. At the follow up visit two weeks later, the patient was doing well. His home glucose monitoring showed fasting blood sugar ranging between 4.4 and 6.5 mmol/l and 2 h postprandial readings between 8 and 10 mmol/l. The triglyceride level becomes normal (1.72 mmol/l).
Conclusion
This patient is likely suffering from T2DM supported by detectable C-peptide level and negative pancreatic auto-antibodies in addition to strong family history of T2DM. Our report stresses that DKA, AP, and HTG can be a rare presentation of T2DM.

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P352

The *TLR3* rs3775291 and rs13126816 polymorphisms are associated with risk for developing T1DM

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Introduction
Viral pathogens seem to play a role in triggering the autoimmune destruction that leads to type 1 diabetes mellitus (T1DM) development. Toll-like receptor 3

(TLR3) has been shown to recognize double-stranded RNA, a molecular signature of most viruses. It is expressed at high levels in pancreatic beta-cells and immune cells, suggesting a role for it in the T1DM pathogenesis. Therefore, the aim of this study was investigate if *TLR3* polymorphisms are associated with T1DM.
Methods
Frequencies of the *TLR3* rs11721827, rs13126816, rs5743313, rs7668666 and rs3775291 polymorphisms were analyzed in 449 T1DM patients and in 507 non-diabetic subjects from South Brazil. Linkage disequilibrium (LD) among *TLR3* polymorphisms were calculated using |D'| and r^2 measurements. Haplotypes constructed from the combination of these polymorphisms were inferred by using a Bayesian statistical method.
Results
Any significant LD was found between all pairs of combination of the five analyzed polymorphisms. The rs3775291G and rs13126816G alleles were more frequent in T1DM patients than in nondiabetic subjects (rs3775291: 0.73 vs 0.67 ($P=0.0001$); rs13126816: 0.70 vs 0.62 ($P=0.001$)). These associations were stronger for the additive model of inheritance (rs3775291: OR = 2.3 (95% CI 1.3–4.2); rs13126816: OR = 2.1 (95% CI 1.3–3.1)). Interestingly, the frequency of T1DM was higher as more risk alleles of the five polymorphisms were present in the haplotype (P-trend = 0.001). Moreover, in T1DM patients, the minor alleles of the rs5743313 and rs117221827 polymorphisms were associated with an early age at diagnosis and worse glycemic control ($P<0.05$).
Conclusion
The *TLR3* rs3775291 and rs13126816 polymorphisms are associated with risk for developing T1DM, while the rs5743313 and rs11721827 polymorphisms are associated with an early age at T1DM diagnosis and worst glycemic control. The number of risk alleles of the *TLR3* polymorphisms in the haplotypes seems to influence the risk for T1DM, suggesting that these polymorphisms might interact in the susceptibility for the disease.

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P353

Association between Asp299Gly and Thr399Ile polymorphisms in *TLR4* gene and type 2 diabetes mellitus: Case-control study and meta-analysis

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Introduction
Polymorphisms in genes that encode proteins of the innate immune system, such as the toll-like receptor 4 (*TLR4*), could affect the immune response as well as the prevalence of type 2 diabetes mellitus (T2DM). Activated TLR4 induces expression of a spectrum of proinflammatory cytokines, which have been implicated in insulin resistance. Some studies have reported associations of the *TLR4* Asp299Gly and Thr399Ile polymorphisms with T2DM. However, other studies have failed to confirm the associations. Thus, this paper describes a case-control study and a meta-analysis conducted to attempt to determine if these two *TLR4* polymorphisms are associated with T2DM.
Methods
The case-control study enrolled 1,683 T2DM patients and 584 non-diabetic subjects from Brazil. A literature search was conducted in order to identify studies that investigated associations between the referred *TLR4* polymorphisms and T2DM. Pooled odds ratios (OR) were calculated for allele contrast and dominant inheritance models.
Results
In the case-control study, genotype and allele frequencies of the Asp299Gly and Thr399Ile polymorphisms differed between T2DM patients and non-diabetic subjects ($P<0.05$). Moreover, the presence of the minor alleles of these polymorphisms were significantly associated with protection for T2DM, after adjusting for ethnicity, under a dominant model (Asp299Gly: OR = 0.68 (95% CI 0.49–0.94); Thr399Ile: OR = 0.65 (95% CI 0.46–0.90)). Seven studies were eligible for inclusion in the meta-analysis. Meta-analysis results showed that the Asp299Gly polymorphism was associated with T2DM protection (OR = 0.68 (95% CI 0.46–1.00), allele contrast model). Stratification by ethnicity revealed that both polymorphisms were associated with T2DM protection under allele contrast and dominant models in Brazilian population but not in Europeans.
Conclusions
In our case-control study, we were able to demonstrate a possible association between the *TLR4* Asp299Gly and Thr399Ile polymorphisms and protection for T2DM. In agreement, our meta-analysis detected a significant association between the 299Gly allele and T2DM protection.

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P354

Age and gender characteristics of carbohydrate metabolism disorders in dependance on HbA1c level

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Diabetes mellitus type 2 (DM type 2) is characterized by constant increase in the number of cases. The worst consequence of this disease is the increase in mortality from injuries of the cardiovascular system. And the best prevention of this complication is active detection and then intensive treatment of DM type 2. Our study is aimed at active detection of patients with impaired glucose metabolism in different regions of Ukraine with help of determination of HbA1c level in the venous blood.
Material's research
HbA1c level was determined in 1564 inhabitants of various regions of Ukraine: Center, West, South-East, North and South.
Results
Depending on age patients were classified as follows: under 45 years – 20%; 46–59 years – 37%; 60–74 years – 30%; over 75 years – 12%. And according to male/female ratio in each age group: up to 45 years – 44 and 56%; 46–59 years – 40% and 60%; 60–74 years – 18 and 82%; and over 75 years – 36 and 64%.
First, it is worth underlying that only 30% of invited people agreed to be examined. Among them we have had the following results of HbA1c level: 6.1–6.4% were observed in 12% of cases, and higher than 6.5% in 16% of the investigated people. And it was figured out that 67% of these studied people had first-line relatives with diabetes mellitus. The majority of males with disordered carbohydrate metabolism was found in the age group 60–64 years; and females – 65–74 years.
Conclusions
i) In Ukrainians of older age groups active detection of DM type 2 by determination of HbA1c level revealed slight carbohydrate metabolism disorders in 12% and evident disorders in 16%.
ii) Not more than 30% of invited people were interested in active detection of DM type 2.
iii) Relatives of patients with diabetes mellitus were mostly interested in this active detection.

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P355

Prevalence of bronchial asthma in patients with type 2 diabetes mellitus

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Background
Bronchial Asthma is characterized by inflammation and airway hyperesponsiveness, which results in episodic airflow obstruction. A relationship between inflammation and insulin resistance has been previously noted and asthma is known to correlate with insulin resistance.
Aim
The aim of this study is to evaluate the prevalence of asthma in type 2 DM patients,presented in 'IKEDA' Hospital, in the period of time January 2010–December 2012.
Patients and methods
We examined all patients diagnosed with type 2 DM. We excluded patients taking other medications than antidiabetics, with familial history of asthma or other illness, and patients with any allergic risk factors. Type 2 DM has been diagnosed according to WHO criteria of 1985, and Bronchial Asthma was diagnosed with the use of GINA criteria.
Results
The total number of Type 2 diabetic patients was 240, of which 150 females and 90 males. The mean age was 58,5 (range 43–74 years old). 32 cases (13.3%) of the total number resulted with Bronchial Asthma. Most cases of them were evidenced in females, in the group-age of 50–60 years old, in patients with older history of diabetes and with/or higher BMI.

The most important result is the fact that the prevalence of asthma is lower in diabetic patients taking antiinsulin resistance therapy, as biguanides and thiazolidinediones.
Conclusion
Bronchial asthma is common in Type 2 diabetic patients, especially in those with higher BMI, that is related to high insulin resistance. This fact should be considered in these patients in the clinical practice.

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Prevention of cardiovascular lesions by active detection of diabetes mellitus

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Among diseases with impaired carbohydrate metabolism, DM type 2 takes first place. And one of the main complications of this non-communicable disease is cardiovascular lesions. Our joint Ukraine-Poland research to actively detect DM type 2 took place during the Euro-2012, where we examined Hb1Ac in different ages of the population in both countries. In Ukraine the study involved 1564 individuals who where tested although they considered themselves free of DM. Their ages varied from 18 to 90 years with the following percentage scheme: 20% - up to 45 years (male-44%); 37% - 46–59 years (male-40%); 31% - 60–74 years (male-18%) and 12% - over 75 years (male-36%). We were directed by the following criteria: Hb1Ac level up to 6% - normal; Hb1Ac level 6.1 to 6.4% - belong to the prediabetic group, Hb1Ac level more than 6.5% - were considered potential patients with DM type 2. The study of people with excessive Hb1Ac content showed the following figures. Male: age group 45 years - Hb1Ac - 6.1–6.4%–50%, Hb1Ac - more than 6.5% –50%; age group 46–59 years was 30 and 70% respectively; age group 60–74 years - 18 and 82%; age group 75–90 years - 50 and 50%. Female: age group of 45 - 50 and 50%; age group 46–59 - 40% and 60%; age group 60–74 years - 36 and 74%; age group 75–90 years - 14% and 86%. The survey results show that carbohydrate metabolism disorders with the Hb1Ac parameters, typical to DM type 2, increase in accordance with age reaching the maximum at 60–74 years in male group and 75–90 years in female group. In this cohort study of tested people - 72% were healthy subjects with Hb1Ac level less than 6%. In 12% - Hb1Ac level within 6.1–6.4%, these people require careful monitoring and preventive measures for DM type 2. In 16% - Hb1Ac level was higher than 6.5% reaching sometimes 8%, this group requires additional studies for revealing DM type 2. Active treatment of these patients would help to serve as secondary prevention of cardiovascular lesions. In this study the Hb1Ac more than 6.5% was found in 16% of tested people. Number of patients with Hb1Ac more than 6.5% increases with age and is highest in males of the age group 60–74 years and females of the age group 75–90 years. Considering the fact that not all invited people agreed to be tested, draws attention that Ukrainians is not very enthusiastic towards necessary research to actively detect DM.

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P357

Screening on type 2 diabetes mellitus incidence in Tashkent

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Background and aims
Progradient course of diabetes mellitus as well as inevitable onset and progression of its late complications having polyorganic character, causing polymorbidity and high mortality of the patients underlie medical–social significance of the problem.
Materials and methods
We examined 784 persons (36% men and 64% women, mean age 53 and 51 years respectively) at high risk of diabetes mellitus onset and progression being screened in 5 locations in Tashkent. The examinees filled up a questionnaire, having their anthropometric parameters, such as, height, weight, waist and hip circumference, assessed and blood taken for measurement of glycemia by means of glucometer.
Results
Random examination helps detecting type 2 diabetes mellitus in 26 persons (4.3%), mean level of glycemia being quite high (8.9 mmol/l). Analysis of enquiring demonstrated that 87% of the examinees were aware of diabetes: 5.8 and 24% of them got information at work and from the media, respectively, 47 and 10.2% being respectively informed by relatives and a physician. Among persons with newly diagnosed diabetes mellitus, the disease is an inherited burden in 53%. Despite available information, the missed cases of hyperglycemia and diabetes in the population indicate lack of awareness and insufficient knowledge about DM.
Conclusions
In the course of random examination hyperglycemia incidence in the adult population of Tashkent (>17 years of age) was found to be 1.4%; type 2 diabetes mellitus was diagnosed in 4.3% of the examinees to serve as the evidence for insufficiency of measures in DM diagnosis. Analysis of enquiring demonstrated inherited burden in 53%, 87% of the examinees being informed about the disease by their relatives (47%) and coworkers (24%). To increase early DM diagnosis awareness the measures should be more adequate.

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Epidemiology of type 1 diabetes mellitus in children in Uzbekistan

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The work was initiated to assess and monitoring of basic epidemiological parameters of type 1 DM among children in the course of the 2000–2007 National Register. Epidemiological data was studied on the basis of annual reports from 13 regional endocrinological dispensaries and Tashkent endocrinological dispensary as well as on the basis of register cards filled up by local endocrinologists–pediatricians. In Uzbekistan within the period from 2000 to 2007 type 1 DM prevalence increased from 7.5 to 11.0 per 100 000 of pediatric population. The highest prevalence was observed in Tashkent (17.7), in Bukhara region (16.6) and in Tashkent region (14.5), the lowest one in Kashkadarya region (7.1) and in Surkhandarya region (7.7). Pediatric incidence in 2007 as compared with 2000 reduced from 2.7 to 2.1 per 100 000 of pediatric population. Analysis of pediatric incidence in 2007 revealed the highest one in Tashkent (4.6) and in Syrdarya region (2.7), the lowest being found in Navoi region (0.9). As to age distribution children aged from 10 to 14 comprised the largest group (66.6%), the smallest including children from 0 to 4 years (5.0%), 28.3% accounting for patients aged from 5 to 9. As to the disease duration children with type 1 DM duration less than 5 years comprised the largest group (70.9%), in the smallest one (2.1%) including patients with 10-year DM duration. As a whole, in Uzbekistan within the period of the Register fulfillment mortality level reduced from 0.1 to 0.03 per 100,000 of pediatric population. In 2007 mortality cases were registered in Kashkadarya region (0.1), Navoi region (0.4) and Samarkand region (0.09 per 100,000 of pediatric population. As a whole in Uzbekistan mortality reduction in children with type 1 DM within the period from 1998 to 2007 was 99%. Within the period of the National Register reduction in mortality paralleling alterations in structure of death cause and increase of survival can be noted to suggest perfect choice of strategy and tactics of the Register fulfillment.

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P359

The rs1746661 polymorphism in the *FNDC5* (Irisin) gene is associated with increased levels of total cholesterol in white patients with type 2 diabetes mellitus

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Introduction
Type 2 diabetes mellitus (T2DM) is a highly prevalent chronic metabolic disease with strong co-morbidity with obesity and cardiovascular diseases. *FNDC5* gene encodes a type I membrane protein that is processed proteolytically to form a newly identified hormone secreted into the blood, termed irisin. After induction by exercise, irisin activates profound changes in the subcutaneous adipose tissue, stimulating browning and *UCP1* gene expression. This causes a significant increase in total body energy expenditure and resistance to obesity-linked insulin resistance. Thus, polymorphisms in the *FNDC5* gene might be associated with T2DM and related disorders.

Objective
To evaluate the association of the *FNDC5* rs3480 (G/A) and rs1746661 (G/T) polymorphisms, individually or in combination, with T2DM or its clinical features.
Methods
We analyzed 1,006 T2DM patients and 431 nondiabetic subjects. Polymorphisms were genotyped by RT-PCR using TaqMan MGB probes. Haplotypes constructed from the combination of rs1746661 and rs3480 polymorphisms were inferred using the Phase 2.1 program.
Results
Genotype and allele frequencies of the rs1746661 and rs3480 polymorphisms did not differ significantly between nondiabetic subjects and T2DM patients ($P>0.05$). Both polymorphisms are in partial linkage disequilibrium ($|D'|=0.88$; $r^2=0.235$). Haplotype frequencies also did not differ among nondiabetic and T2DM groups ($P=0.913$). T2DM patients carrying the rs1746661 T allele had increased levels of total cholesterol when compared with the G/G genotype (T/T-G/T: 212.4±47.6 G/G: 203.8±47.2 mg/dl; $P=0.023$) after adjustment for covariates. Furthermore, patients carrying the mutated haplotype in homozygosis had increased levels of total cholesterol ($P=0.014$) as well as increased risk of hypercholesterolemia (OR=1.49 (1.01–2.19); $P=0.046$), after adjustment for covariables.
Conclusion
This study showed no association between the rs1746661 and rs3480 polymorphisms and T2DM; however, the rs1746661 polymorphism was associated with increased levels of total cholesterol.

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Atherosclerosis in patients with prediabetes and type 2 diabetes is associated with more significant microcirculation abnormalities

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It is known that patients with prediabetes (impaired glucose tolerance and impaired fasting glucose) ant type 2 diabetes (T2D) have micro-and macrovascular complications. It may be assumed that vascular changes begin in the smallest vessels that leads to microcirculation abnormalities.
Purpose
To estimate microcirculation abnormalities in patients with prediabetes and T2D and concomitant atherosclerosis.
Materials and methods
One hundred and eighty-one patients were divided into five groups: 1–27 patients with prediabetes, 2–28 patients with prediabetes and concomitant CHD (effort angina, functional class 1–2), 3–20 patients with prediabetes and concomitant CHD and atherosclerosis, 4–47 patients with T2D and concomitant CHD and 5–59 almost healthy person. Microcirculation was measured by computer based conjunctival biomicroscopy (Malaja *et al.*), results were evaluated by the set of criteria for quantitative evaluation of conjunctival microcirculation: FC (number of active capillary tubes), AVA (arteriovenous anastomosis), Mean (vascular tortuosity), Sl (sludge), Mtr (microthrombosis). Severity of each criteria was scored, more severy changes had higher degree.
Results
Increased Mean were revealed in patients with prediabetes (0.37±0.039) without concomitant CHD compared to almost healthy person (0.27±0.009, $P<0.05$). In patients with concomitant CHD (group 2) and atherosclerosis (group 3) microcirculation abnormalities consist in Mean (0.4±0.039, 0.5±0.048 correspondingly), development of Sl (2.4±0.22, 2.5±0.24 correspondingly vs 1.81±0.05) and development of Mtr (2.2±0.15, 2.08±0.14 correspondingly vs 0.72±0.006) compared to almost healthy person ($P<0.05$, $P<0.01$ – $P<0.001$; $P<0.001$, $P<0.01$ – $P<0.001$ correspondingly). The lowest number of FC was revealed in patients with T2D and CHD (2.77±0.11) compared to group 5, (1.94±0.06, $P<0.001$).
Conclusion
Minimal microcirculation abnormalities were revealed in patients with prediabetes without concomitant diseases. In the presence of CHD or atherosclerosis intensity of symptoms increases. Maximal changes were revealed in patients with T2D and CHD.

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Relationship between indices of nutriture among residents of a Coastal City in South East Nigeria

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Background
There is a relationship between the indices of nutriture-BMI, waist circumference (WC), waist–hip ratio (WHR) and the development of glucose intolerance.
Objectives
To determine the normative values of the indices of nutriture and the inter relationship between these indices in male and female residents of a Calabar, South East Nigeria.
Methods
A sample comprising 1134 subjects (645 males and 489 females) representative of the entire population of Calabar metropolis aged 15–79 was studied. A multistage sampling method was applied to select the subjects for the study which involved the selection of four wards by randomization from the 22 wards of Calabar City and 50 house-holds from each of the four wards were selected using the table of random numbers, out of which eligible individuals aged between 15 and 79 years from the 200 households selected were recruited. Information obtained included anthropometric indices (height in meters, weight in kilogram, waist circumference in centimetre, Hip circumference in centimetre). Anthropometric indices were expressed as mean (S.D.). The comparison of means between groups was done using independent Student's *t*-test and the strength of association between quantitative variables by using the Pearson's correlation coefficient. The normative values of indices of nutriture were determined using confidence interval, and the level of significance was taken as $P<0.05$.
Results
There is strong positive linear relationships between all indices of nutriture but the relationship was strongest between WC and BMI ($r=+0.70$, $P<0.01$), followed by WHR and BMI ($r=+0.65$, $P<0.01$ then WC and WHR ($r=+0.49$, $P<0.01$).
Conclusion
The strongest relationship was between waist circumference and BMI and both have significant bearing on glucose intolerance.

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Pregnancy outcomes in women with gestational diabetes

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Introduction
Although diagnostics and therapy are much improved over the years, women with gestational diabetes still have more adverse course and outcome of pregnancy than healthy women. Their pregnancies are more often complicated with the different forms of maternal and fetal morbidity. Our study investigates all cause early neonatal morbidity (neonatal jaundice, neonatal hypoglycemia, fetal distress syndrome and other) and newborns maturity and vitality in the groups of delivered gestational diabetes and healthy women.
Methods/design
Retrospective study included 96 delivered gestational diabetes women and 106 delivered healthy women. We analyzed age of delivered women, incidence of caesarian section, gestational week at the time of delivery, Apgar score in first and 5th min, birth weight and length and incidence of all cause early neonatal morbidity in two groups. In statistical analysis we used mean values, proportions, *t*-test and test of proportions.
Results
There were no significant differences in age of women and incidence of caesarian section. Women with gestational diabetes gave birth at earlier gestational week ($P=0.0455$). Both Apgar scores were lower in newborns of delivered gestational diabetes women ($P=0.0182$; $P=0.0012$). Birth length was greater in newborns of delivered gestational diabetes women ($P=0.0309$) and difference in birth

weight was on border of statistical significance ($P=0.0561$). All cause early neonatal morbidity had higher incidence in newborns of gestational diabetes women ($P=0.0014$).
Conclusion
Current guidelines for the screening on gestational diabetes during the pregnancy enabled timely diagnosis and adequate treatment of this condition. This allowed gestational diabetes women to carry their pregnancy almost similar as healthy women. However, offspring of gestational women still tends to be macrosomic, so these women deliver at earlier gestational week than healthy women. Their newborns earn lower Apgar score and the incidence of all cause early neonatal morbidity in this group is greater comparing to delivered healthy women.

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P363

Intensive and expensive new treatments or better education for patients with diabetes: Where should we begin with?

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Design and methods
Though several new treatments for diabetes (DM) are available, their effectiveness, however, might be limited, by patients knowledge. In order to test patients' knowledge and self-management of diabetes, we had employed a questionnaire for clinic patients with types 1 and 2 DM. This was a pilot study for a telemetric medicine EU project (www.COMMODITY12.eu). Study involved 37 subjects (19 males) with type 1 ($n=18$) or insulin treated type 2 DM ($n=19$), who attended Diabetes Clinic in Lodz, Poland. All patients with type 1 DM and 10/19 (53%) patients with type 2 DM were using intensive insulin therapy, while 6/18 (33%) patients with type 1 DM were using insulin pumps
Results
Patients with type 2 DM were older than patients with type 1 DM (62 ± 11.7 years vs 27 ± 9.4 years, $P<0.001$). Though HbA1c concentrations were seemingly almost identical in patients with type 1 *vs* those with type 2 DM ($7.2\pm0.78\%$ vs $7.32\pm1.1\%$), in fact 11/19 patients with type 2 DM (58%) could not recall any recent HbA1c value. There was a major difference in attitude towards diabetes in terms of glucose monitoring or insulin dose adjustments between patients with type 1 and type 2 DM, as illustrated in the table.
Conclusions
Overall knowledge of patients with diabetes, and particularly with insulin treated type 2 DM, remains highly inadequate. Though advances in modern therapies are important, they are unlikely to provide expected impact without going 'back to basics', i.e. greater emphasis on patient education and monitoring.

Table 1

Glucose monitoring (*n* (%)) (*denotes $P<0.05$, for DM t.1 versus DM t.2)		
4–5 times/day	DM t.1: 15 (83%)*	DM t.2: 8 (42%)*
2–3 times/day	3 (17%)	6 (32%)
Once a day or less	–	5 (26%)

	Yes	No	Yes	No
I try to adhere to diabetic diet	9 (50%)	9 (50%)	12 (63%)	7 (37%)
Count carbohydrate exchange units	12 (66%)	6 (34%)	5 (26%)	14 (74%)*
Perform systematic physical exercise	8 (44%)	10 (56%)	7 (37%)	12 (63%)
Avoid physical activity	7 (39%)	11 (61%)	12 (63%)	7 (37)*
Adjust insulin doses according to preprandial glycaemia	17 (94%)	1 (6%)	8 (42%)	11 (58%)*
Adjust insulin doses according to postprandial glycaemia	8 (44%)	10 (56%)	5 (26%)	14 (74%)
Adjust insulin doses according to how much I eat	15 (83%)	3 (17%)	7 (37%)	12 (63%)*
Adjust insulin doses according to planned physical activity	15 (83%)	3 (17%)	4 (21%)	15 (79%)*
Change insulin doses according only with doctor consent	1 (6%)	17 (94%)	12 (63%)	7 (37%)*

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P364

Does systematic error in the HbA1c measurement matter when locally analyzed HbA1c is used for benchmarking in a national diabetes register?

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Introduction
HbA1c is an important quality indicator when benchmarking diabetes clinics. Systematic error in the measurement of HbA1c could result in inappropriately high or low values, and if not corrected give a wrong impression of the standard of care.
Methods
We included data on HbA1c from the Norwegian adult diabetes register on 3,854 type 1 diabetics attending 13 hospital clinics. Correction factors for HbA1c were derived from the results of the local laboratories' quarterly external quality assessment scheme. These factors were used to correct the patient yearly median HbA1c before the corrected clinic median HbA1c was calculated
Results
Before correcting the clinic median HbA1c, values varied from 7.7 to 8.6%, and after correcting from 7.8 to 8.2%. Compared to the uncorrected values, the corrected values were within $\pm0.2\%$ for all but one clinic whose median HbA1c was reduced with 0.4%. After correction the overall percentage of type 1 diabetics with poor glycemic control (HbA1c $>9.0\%$) was reduced from 23.9 to 21.0%. One clinic reduced the percentage with 11% and two clinics with 5% whereas to clinics increased the percentage of patients with poor glycemic control with 5% after correction.
Conclusion
For six out of 13 clinics, correcting HbA1c values changed the percentage of patients with poor glycemic control, and one clinic reduced its median HbA1c substantially. Our results suggest that knowledge of the systematic error in the HbA1c measurement is important for correct interpretation of benchmarking results if HbA1c is measured at local laboratories.

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P365

***UCP1*, *UCP2* and *MnSOD* expression in pancreas from brain-death subjects: A case-control study**

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Introduction
Long-term insulin independence after pancreatic islet transplantation depends on the engraftment of a large number of viable islets. However, the yield and quality of islets isolated from brain-death (BD) donors are negatively affected by upregulation of proinflammatory cytokines and by hypoxia and oxidative stress that occurs during the BD status. Uncoupling proteins (UCPs) are mitochondrial transporters present in the inner mitochondrial membrane and are associated with protection against oxidative stress. Manganese superoxide dismutase (MnSOD) enzyme is the first line of defense against oxidative stress in mitochondria. Thus, we compared pancreatic gene expressions of *UCP1*, *UCP2* and *MnSOD* between BD-organ donors and control subjects who undergone therapeutic pancreatectomy. The expressions of these genes were also evaluated in a murine model of BD.
Methods
Human pancreatic tissue biopsies were collected from 15 cases of BD and 17 controls, while rat pancreatic biopsies were obtained from 7 BD rats and 6 controls. Pancreatic *UCP1*, *UCP2* and *MnSOD* gene expressions were evaluated by RT-qPCR.
Results
Brain-death organ donors had higher pancreatic mRNA concentrations of *UCP1* and *UCP2* in comparison to control subjects (*UCP1*: 0.55 ± 0.54 vs -0.38 ± 0.52 n fold change ($P=0.001$); *UCP2*: 0.36 ± 0.20 vs -0.39 ± 0.81 ($P=0.012$)). Accordingly, pancreatic *Ucp2* mRNA concentrations were higher in BD rats than in control rats (0.41 ± 0.22 vs 0.04 ± 0.21 ($P=0.013$)). *Ucp1* mRNA was not detected in the murine pancreas. Human *MnSOD* mRNA levels were similar in pancreas from BD cases and controls; however, murine *Mnsod* expression was higher in the pancreas of BD rats compared to controls (0.15 ± 0.32 vs -0.22 ± 0.32; $P=0.037$).
Conclusion
UCP1-2 expressions seem to be affected by BD of organ donors. Further studies are necessary to evaluate the role of these proteins in the modulation of BD-induced oxidative stress in the pancreas.

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P366

Association between UCP polymorphisms and BMI changes: A cross-sectional study and meta-analysis

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Aims
Some studies have reported associations between uncoupling protein (*UCP*) 1–3 polymorphisms and obesity or related-features. However, other studies have failed to confirm these associations. Thus, this study describes a cross-sectional study and a meta-analysis conducted to attempt to determine whether the -3826A/G (*UCP1*), -866G/A, Ala55Val and Ins/Del (*UCP2*) and -55C/T (*UCP3*) polymorphisms are associated with body mass index (BMI) in patients with type 2 diabetes mellitus (T2DM).
Methods
The cross-sectional study enrolled 767 T2DM patients, all of European ancestry. A literature search was conducted in order to identify all studies that investigated associations between *UCP*1–3 polymorphisms and BMI. Weighted mean differences (WMD) were calculated for additive, recessive, dominant and co-dominant inheritance models.
Results
In the cross-sectional study, mean of BMI did not differ significantly according to the different genotypes of *UCP*1–3 polymorphisms ($P>0.05$). Fifty-five studies were eligible for the meta-analysis. Meta-analysis results showed that the *UCP2* -866 and Ala55Val polymorphisms were associated with increased BMI in Asian and European population, respectively (866: WMD=0.10 (95% CI 0.04–0.16) for the co-dominant model; Ala55Val: WMD=0.39 (95% CI 0.02–0.75) for the dominant model]. Moreover, the *UCP2* Ins/Del polymorphism was associated with increased BMI in Asians (WMD=0.46 (95% CI 0.14–0.77), dominant model). In contrast, the *UCP2* -866 polymorphism was associated with decreased BMI in Europeans (WMD= −0.17 (95% CI −0.33–−0.01), for the dominant model). There was no significant association of the *UCP1* -3826A/G polymorphism with BMI mean differences.
Conclusions
In our cross-sectional study we were not able to demonstrate any association between the *UCP* polymorphisms and BMI. However, our meta-analysis detected a significant association between the *UCP2* -866G/A, Ins/Del, Ala55Val and *UCP3* -55C/T polymorphisms and BMI mean differences.

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P367

Serum cytokines and proinflammatory markers in first degree relatives of patients with type 1 diabetes

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Background and aims
In patients with type 2 diabetes, elevated tumor necrosis factor α (TNFα), C-reactive protein (CRP), chemerin, fetuin-A, have been reported. However, it is not entirely clear whether these alterations in adipokine serum concentrations are already present in prediabetic states and in type 1 diabetes. The aim of the study was to investigate whether adipokine profiles (chemerin, fetuin-A, TNFα) and inflammatory markers (CRP) are associated with decreases in insulin sensitivity and beta cell function in first degree relatives of patients with type 1 diabetes (T1D) and their usefulness in the assessment of the risk of development of diabetes.
Material and methods
The study was conducted in 90 first- degree relatives of the patients with T1D (mean age 27.1±15.48 years; mean BMI 24.6±4.95 kg/m^2) and 60 healthy individuals (mean age 29.9±13.7 years; mean BMI 22.8±2.3 kg/m^2). TNFα, chemerin and fetuin-A concentrations were determined using ELISA method, CRP by turbidimetric method. HOMAIR and HOMA%B indices were calculated using computer calculator from the Website Oxford Centre for Diabetes, Endocrinology and Metabolism.
Results
CRP and TNF-alpha concentrations were significantly higher in the relatives compared to the controls (3.27±2.48 vs 1.14±1.39 mg/l; $P<0.007$; 8.58±15.49 vs 0.63±0.79 pg/ml, $P<0.005$ respectively). We found significantly higher chemerin concentration (0.6848±28.67 vs 0.5112±32.41, $P<0.006$) and fetuin-A concentration (276.92±30.9 vs 214.66±34.2; $P<0.001$) in the study group as compared to the healthy controls. Significantly higher HOMAIR (1.16±0.63 vs 0.79±0.34, $P<0.002$) and significantly lower HOMA%B index (92.84±29.39 vs 114.0±47.06, $P<0.015$) were found in the relatives as compared to the controls. HOMAIR correlated positively with TNFα ($r=0.430$, $P<0.001$), chemerin (0.732, $P<0.0001$) fetuin-A (0.454, $P<0.0001$) and CRP ($r=0.445$, $P<0.0001$). HOMA%B negatively correlated with TNFα ($r=-0.431$, <0.0001) and CRP ($r=-0.460$; $P<0.0001$).
Conclusions
Alterations in chemerin, fetuin-A, CRP and TNFα are already detectable in first degree relatives of T1D, and may reflect to identify insulin resistance as an early pathogenetic event before T1D development. Fasting levels of chemerin, fetuin-A, CRP and TNFα probably will be used as biomarkers to identify insulin resistance and decrease of beta cell function in healthy individuals with higher risk of T1D.

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Increased prevalence of anti-thyroid and anti-gastric parietal cell antibodies in first degree relatives of patients with type 1 diabetes

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Aim
It is well known that T1D is associated with other autoimmune diseases. The aim of this study was to compare the prevalence of various auto-antibodies in first-degree relatives of patients with T1D and healthy individuals with negative family history of diabetes.
Material and methods
The group studied consisted of 90 relatives and 60 healthy individuals. Serum concentrations of antibodies to anti-21-hydroxylase (21-OH-Abs), anti-gastric parietal cell antibodies (GPC-Abs), anti-thyroglobulin antibodies (TG-Abs), anti-thyroid peroxidase antibodies (TPO-Abs) and anti-TSH receptor antibodies (TSHR-Abs) were measured by commercial radioimmunoassay.
Results
Positive antibodies against pancreatic islet antigens were found in 34.4% of the relatives (IAA in 23.3%, GADA in 16.7% and IA-2A in 2.2%) and in none of the controls. Other antibodies (mainly TPO-Abs, TSHR-Abs and GPC-Abs) were detected in 40% of all relatives and in 93.5% of these with positive anti-islet antibodies. Median levels of 21-OH-Abs, GPC-Abs, TPO-Abs and TSHR-Abs were significantly higher in the relatives, in particular these with positive anti-islet antibodies, as compared with the group of relatives with no anti-islet antibodies and the controls. A positive correlation between IAA and TPO-Abs levels was noted in the whole group of relatives, as well as in a subgroup with anti-islet antibodies ($r=0.549$, $P<0.05$ and $r=0.567$, $P<0.05$ respectively).
Conclusions
Our results demonstrated for the first time significantly higher prevalence of anti-thyroid antibodies and anti-gastric parietal cell antibodies in the first degree relatives of T1D patients, in particular in these with positive anti-islet antibodies. The finding suggest that these subjects may be at higher risk of developing not only type 1 diabetes, but also other autoimmune disorders and should be routinely screen especially for autoimmune thyroid disease and auto-immune gastritis.

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P369

Sexual function of 26–36-year-old men with type 1 diabetes

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Sexual dysfunction of type 1 diabetic (T1D) men is an area that has been rarely investigated until now. Investigation of reproductive health of young men was performed in Nordic and Baltic countries in 2003/2004 ('The Reproductive function of Estonian, Latvian and Lithuanian young men' (ELLY)) but analysis of

sexual function was out of the target of the study. In this study we invited those presumably healthy men to participate as controls for investigation of T1D men sexual function.
We investigated the structure of sexuality of 26–36-year-old T1D men comparing them with the same age healthy men from ELLY.
One hundred and twenty-two T1D and 80 ELLY men filled the European male ageing study-sexual function questionnaire (EMAS-SFQ) and 4 domains of sexual function were calculated according to EMAS: overall sexual functioning (OSF), masturbation score (MS), sexual-function-related distress (SFD), change in sexual functioning during 1 year (CSF).
MS is lower in T1D men (1.29 ± 1.62 vs 2.27 ± 1.94 (T1D vs ELLY, M $\pm$ SD)). Difference of SFD appears when disease duration is 5–9 years (3.68 ± 3.77 vs 1.42 ± 1.93) and extremely increases later while difference of OSF manifests when T1D duration is 10–19 years (19.24 ± 5.34 vs 21.20 ± 5.62). CSF does not appear in any group. SFD is the only domain that differs and is higher in patients with proliferative retinopathy in comparison with non-proliferative retinopathy (5.18 ± 4.93 vs 1.20 ± 1.76).
Decrease of MS in T1D from the beginning of the disease cause a doubt if it is a real complication in contrast to slowly increasing SFD and decreasing OSF when the duration of T1D increases.
Majority of ELLY and T1D men had permanent sexual partners so increase of MS in healthy men cannot be attributed to the lack of sexual partner. Contrary may be truth: they have the only partner for long time and masturbation satisfies their unmet sexual needs ('price for fidelity').

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P370

Compensatory increased irisin levels in gestational diabetes mellitus

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Context
Irisin, a newly discovered hormone, is secreted by skeletal muscles into circulation. It is proposed to regulate energy homeostasis and hold therapeutic potential in diabetes and obesity.
Objective
We aimed to investigate the association of irisin and uncoupling protein 1 (UCP1) with gestational diabetes mellitus (GDM).
Design and Setting
This was a cross-sectional study conducted in a university hospital.
Participants
A total of 61 pregnant women (30 GDM; 31 non-GDM) along with 41 age-matched non-pregnant controls participated in the study.
Main Outcome Measures
Plasma irisin, serum UCP1, insulin, fasting blood glucose (FBG), high sensitivity C-reactive protein (hs-CRP), and lipids were measured.
Results
Irisin levels were significantly higher and UCP1 levels lower in the GDM group, compared with both the non-GDM and the control groups ($P<0.001$). Irisin was inversely correlated with UCP1 ($r=-0.42$, $P<0.001$) and positively correlated with body mass index (BMI; $r=0.25$, $P=0.008$), hemoglobin A1c ($r=0.22$, $P=0.026$), homeostasis model assessment of insulin resistance (HOMA-IR; $r=0.22$, $P=0.024$), total cholesterol ($r=0.39$, $P<0.001$), and triglycerides ($r=0.25$, $P=0.010$). UCP1 was inversely correlated with BMI ($r=-0.20$, $P=0.046$), HOMA-IR ($r=-0.25$, $P=0.011$), total cholesterol ($r=-0.27$, $P=0.006$), and triglycerides ($r=-0.29$, $P=0.003$). Logistic regression analysis results indicated that irisin levels were not a significant risk factor for developing GDM. On the contrary, lower UCP1 levels were a risk factor independent of the other factors. Multiple regression analysis showed that BMI and UCP1 levels were directly related to irisin levels.
Conclusion
In patients with GDM, irisin signaling might be impaired leading to a compensatory increase in its levels.

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P371

GCK-MODY caused by a new mutation in the GCK gene

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Introduction
Glucokinase-MODY (Maturity onset diabetes of the young) results from heterozygous mutations in the GCK gene, impairing its enzymatic activity. GCK acts as a glucose sensor in the pancreatic beta cell and regulates insulin secretion. We describe two cases of MODY due to a *GCK* gene mutation not described until now.
Clinical Case
A 63-year-old male is followed in our hospital for 30 years due to diabetes mellitus (DM). He was diagnosed in his twenties and his family history was strongly positive for diabetes (maternal grandmother, mother and two brothers). He always had a good metabolic control (HbA1c 6–6.8%) under oral anti-diabetic medication (currently under metformin and sitagliptin). Nowadays the only complication is an increased albuminuria (92.5 mg/g creatinine) under irbesartan 300 mg/day. His son is 25 years-old and was diagnosed with diabetes at age 4, by routine analysis. Type 1 diabetes-specific antibodies were always negative, as were his father's. He never needed anti-diabetic medication due to good glycemic control (HbA1c 5.3–6.1%), such that he has only been on diet. He has no complications of the disease.
Both clinical presentations were highly suggestive of GCK-MODY, so a sequencing analysis of the *GCK* gene was done on both patients and a c.1318G>T (p.Glu440X) heterozygous loss-of-function mutation encoded on exon 10 was identified. It introduces a premature stop codon in the synthesis of GCK, impairing its activity and likely being a GCK-MODY causing mutation.
Conclusion
There are more than 600 mutations described over the GCK gene, some of them causing MODY. Only a few have been detected in exon 10. We report a heterozygous mutation in the exon 10 of the *GCK* gene still not described in the literature, which results in the typical GCK-MODY phenotype, found in two members of different generations of the same family.

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P372

Branched-chain and aromatic amino acid plasma concentration as a markers of metabolic syndrome

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Results of metabolomic studies showed the relation of branched-chain amino acids (BCAA) and aromatic amino acids (AAA) with metabolic disorders.
Basing on this observation we assessed amino acid profile in 286 professionally active men (aged 36–60 years). 141 of them met the criteria of metabolic syndrome (MS) and remaining 142 served as controls.
Quantitative analysis of BCAA (leucine-LEU, valine-VAL, isoleucine- ILE) and AAA (phenyloalanine-PHE, tyrosine-TYR, tryptophan-TRP) was performed by gas-liquid chromatography connected with mass spectrometry using GLC–MS system.
Lipids, adiponectin (AD) glucose and insulin were measured by standard methods.
Plasma concentration of BCAA and AAA differed significantly between MS(+) and MS(−) groups. By means of principal component analysis (PCA) three factors have been formed (f-BCAA, f-AAA_1 and f-AAA_2). The values of these factors discriminated MS(+) and MS(−) groups – (table).
Logistic regression analysis revealed good efficacy of models consisted of f-AAA1 (OR = 1.23) + f-AAA2 (OR = 1.38), ($P=0.02$) as well as f-BCAA (OR = 1.3) + AD (OR = 0.93) in the classification into MS(+) or MS(−) groups, $P=0.004$). The correlation between Homeostasis Model Assessment (HOMA) and f-BCAA + AD tested using the linear regression was found ($r^2=0.11$, $P=0.001$) with prevalent role of f-BCAA compared to AD.

Results of our study confirmed the association of BCAA and AAA with metabolic disorders. Further studies are justified to elucidate the role of the amino acid metabolism as a possible therapeutic target for insulin-resistance related disturbances.

Table 1

		LEU	VAL	ILE	PHE	TYR	TRP	f-BCAA	f-AAA_1	f-AAA_2
MS(+) n=141	25%	130.2	220.2	58.2	69.1	21.3	45.6	−0.88	−0.62	−0.32
	50%	157.8	275.6	70.4	87.6	27.1	63.8	0.29	0.17	0.23
	75%	182.7	320.0	82.8	103.4	34.7	84.4	0.92	1.11	0.67
MS(−) n=145	25%	115.7	213.8	52.6	65.6	20.3	40.2	−1.08	−0.83	−0.62
	50%	138.5	247.4	60.7	78.1	26.7	54.9	−0.53	−004	−0.12
	75%	197.2	297.2	75.3	92.1	33.9	76.7	0.47	0.53	0.38
P		0.001	0.02	0.001	0.003	0.53	0.05	<0.001	0.10	0.006

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P373

Acromegaly treatment and carbohydrate metabolism disturbances

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Background
In acromegaly, carbohydrate metabolism disorders (CMD) are frequently observed. We aimed to assess the differences in insulin secretion and sensitivity depending on stage of the disease and type of treatment.
Design
Sixty-four patients with acromegaly (46 women; age 53 (interquartile range, IQR 47–59) years), of whom 29 were newly-diagnosed (NA group), 20 treated with somatostatin analogues (SSA group) and 15 after transsphenoïdal surgery (TSS group) participated. All underwent a glucose tolerance test, with measurement of plasma insulin and blood glucose in the fasting state and every 30 min for 2 h after oral administration of 75 g glucose. CMD (impaired glucose tolerance, IGT, impaired fasting glucose, IFG plus diabetes, DM) were diagnosed according to WHO recommendations. We used the Matsuda index and HOMA-IR to estimate insulin sensitivity.
Results
Mean age (48–55 years) and mean BMI (29.2–30.2 kg/m^2) were comparable between the three groups. Z-score IGF1 was similar between the SSA and TSS groups (3.2 (2.4–5.2) vs and 3.5 (0.6–5.7)), but severely elevated in NA patients (P=0.0001). In the SSA group, prevalence of CMD was 90%, whereas it was 62% in the NA group and 27% in TSS group. NA patients were mainly insulin-resistant, with high fasting plasma insulin (FPI) of 93 (IQR 56–196) pmol/l, high HOMA-IR (5.6 (1.9–9.1)) and low Matsuda index. TSS patients had normal FPI (56 (IQR 17–92) pmol/l), and normal HOMA-IR and Matsuda index for their BMI, while SSA patients were mainly insulin-deficient, with FPI 38.0 (14–62) pmol/l, HOMA-IR 1.4 (0.7–3.0) and Matsuda index 7.1 (2.7–9.8).
Conclusion
Hyperinsulinaemia compensates the high level of insulin resistance in NA patients. In SSA patients, suppression of insulin secretion leads to increasing of percentage of DM patients in this group. After TSS, insulin resistance decreases and insulin secretion is restored, that leads to the normalization of carbohydrate metabolism.

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New onset T1DM after vaccination for measles: Coincidence or consequence?

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Introduction
Viruses and virus-induced lymphokines may have an important role in the pathogenesis of autoimmunity. The occurrence and significance of autoimmune manifestations after the administration of viral vaccines remain controversial. Herein we have represented a case who developed type 1 diabetes 1 month after vaccination for measles in military.
Case
A 25-year-old male patient admitted to our clinics with the complaints of polyuria, poydipsia, and weight loss. When we questioned his personal history, we have learnt that he had measles vaccination in the army, 1 month ago. In the initial labaratory examinations, plasma glucose was 400 mg/dl, dipstick urine test was ++++ and there was metabolic acidosis with anion gap. After treatment of diabetic ketoacidosis, we skipped to intensive insulin treatment with short and long acting anologue insulins. Since he had very low C-peptide level together with positive anti GAD and anti-islet antibodies, he was diagnosed to have T1DM. His anti TPO was positive and had thyroiditis on ultrasonography. We have screened other components of autoimmune syndrome and found that celiac markers and antiparietal antibodies were negative. He had adequate cortisol response to short cosyntrophin test. He was discharged after regulation of blood glucose levels.
Conclusion
Very few patients may develop some autoimmune diseases following viral vaccination (in particular; arthropathy, vasculitis, neurological dysfunction, and thrombocytopenia). For the majority of people, vaccines are safe and no evidence linking viral vaccines with type 1 diabetes, multiple sclerosis (MS) or inflammatory bowel disease can be found. However there are rare cases in the literature reporting new onset autoimmune diabetes after vaccination. Therefore, it might be reasonable to screen patients who are prone to diabetes for the signs and symptoms of diabetes after vaccination.

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P375

Adipokines, insulin resistance in early pregnancy and risk for gestational diabetes

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Introduction
Pregnancy is characterized by a progressive insulin resistance (IR). Some, but not all, previously published studies suggest that adipokines are related to insulin resistance in pregnant women and subsequent development of gestational diabetes (GDM).
The aim of this study was to investigate the relation between adiponectin, leptin, its ratio and homeostasis model assessment of IR (HOMA-IR) in the first prenatal visit and whether it could be used to predict the risk of developing GDM.
Methods
One hundred and forty-three women were recruited before 15 weeks of gestation and were followed up until delivery. Maternal plasma adiponectin, leptin concentrations were measured and IR was assessed by HOMA-IR at 8–14 weeks of gestation. 2 h 75 g oral glucose tolerance test (OGTT) was performed between 24 and 28 weeks of gestation. GDM was diagnosed according to IADPSG criteria.
Results
The 124 healthy and the 19 women who subsequently developed GDM had similar levels of adiponectin (P=0.153), leptin (P=0.103) and HOMA-IR (P=0.115).). However the adiponectin/leptin (A/L) ratio was significantly higher in healthy pregnant women than in those who developed GDM (1.01 vs 0.68, P=0.034). We found a significant negative correlation between A/L ratio and HOMA-IR (r=−0.43; P<0.001), adiponectin concentration and HOMA-IR (r=−0.229; P=0.013), adiponectin and leptin (r=−0.286; P=0.001), A/L ratio and BMI before pregnancy (r=−0.666; P<0.001) and a positive correlation between leptin and HOMA-IR (r=−0.43; P< 0.001).

Conclusion
A/L ratio negatively correlates with HOMA-IR in early pregnancy and has a potential of biomarker for the prediction of GDM.

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P376

Prevalence of androgenic deficit in men with metabolic alterations

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Introduction
The syndrome of late-onset hypogonadism (LOH) is a clinical and biochemical syndrome associated with advancing age male, characterized by typical symptoms and decreased serum concentrations of testosterone, which can affect multiple organ systems and may impair quality of life. The prevalence of LOH syndrome is higher in certain patient groups, obese, diabetic and suffering from erectile dysfunction manifest LOH at higher rates than the general population.
Objective
Analyze the prevalence of androgenic deficit depending on total testosterone (TT), calculated free testosterone (cFT), and free androgen index (FAI) in a group of diabetics (DM2), prediabetics (PreD) and nondiabetics (ND).
Material and methods
TT analysis, albumin, and SHBG were performed on 207 samples of men, age 61.5 ± 11.6 years attending in endocrinology consultation. The cFT is calculated using the formula of Vermeulen and also the FAI values obtained by dividing the value of TT by SHBG.
Results
Of the 207 males, 123 are DM2, 24 PreD and 60 ND. The prevalence of androgenic deficit as TT values is overt hypogonadism (TT $<$ 230 ng/dl) in 7.3, 12.5 and 3.3% (without significant differences between the three groups (NS)); mild hypogonadism (TT 230–350 ng/dl) in 31.7, 29.2 and 35%, (NS), and no evidence of hypogonadism (TT $>$ 350 ng/dl) in 61, 58.3 and 61.7% (NS).
In contrast, the prevalence of overt androgenic deficit according to the cFT (cFT $<$ 65 pg/ml) is 29.3, 16.7 and 21.7% ($P < 0.01$, between the three groups). According to the FAI (it's deficient if FAI $<$30), androgenic deficit was 24.4, 8.3 and 8.3% ($P < 0.001$, between DM2 group and the other two groups).
Conclusions
Androgenic deficit is found not only in DM2, but also in PreD, so that it could constitute an independent predictor factor for metabolic syndrome and DM2 in middle-aged men.

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P377

Assessment of relaxin levels in pregnant women with gestational diabetes mellitus

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Introduction
Gestational diabetes mellitus (GDM) is an important co-morbidity of pregnancy, with insulin resistance a key contributor in its underlying pathology. Relaxin is a hormone considered crucial for mediating adaptations deemed vital for maintenance of pregnancy. Evidence has suggested that levels of plasma relaxin may be positively correlated with insulin sensitivity. This led us to hypothesize that relaxin may play a role in the pathogenesis of insulin resistance in women with gestational diabetes. The aim of this study was to assess levels of plasma relaxin in women with GDM compared to a control group of healthy pregnant women in the third trimester of pregnancy.
Design and methods
Twenty-six GDM subjects and 27 healthy controls were recruited, matched for gestation week and age. A blood sample was obtained from all participants to determine plasma relaxin levels during the 3rd trimester of pregnancy. Additional data including age, gestation term and HbA1c was collected. A Mann – Whitney *U* test was used for statistical analysis between the two groups. The study was ethically approved by the Proportionate Review Sub-Committee of North Wales REC. Plasma relaxin was measured by ELISA using kit provided by R and D Systems Europe Ltd.
Results
Plasma relaxin levels in the GDM group were higher compared to the healthy control group (median relaxin concentration 667.5 pg/ml (range = 190–2,450 pg/ml) in GDM group *vs* 439 pg/ml (range = 112–1,185 pg/ml) in control group), although this did not reach statistical significance ($P = 0.15$).
Conclusion
Plasma relaxin levels were found to be higher in women with GDM although not statistically significant. Increased relaxin levels in GDM may be a result of the body's compensatory mechanism to overcome increased insulin resistance present in this group. More studies are required to understand whether relaxin plays a role in the pathogenesis of gestational diabetes and insulin resistance.

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P378

Low serum 25(0H) vitamin D3 concentration is associated with increased accumulation of advanced glycation endproducts (AGEs) in the skin of patients with type 1 diabetes

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Introduction
Influence of vitamin D status on metabolic control of type 1 diabetes (T1DM) remains controversial. The marker of long-term metabolic control that was not evaluated in this context is tissue accumulation of advanced glycation endproducts (AGEs), measured using skin autofluorescence. Aim of the study was to determine the association between serum 25-hydroxyvitamin D3 (25(OH) D3) concentration and accumulation of AGEs in adults with T1DM.
Materials and methods
We included 100 consecutive patients with T1DM (55 men, 45 women) aged 29(6) years (mean(s.d.)) with diabetes duration 13(6) years, 35 had diagnosed at least one microangiopathic complication (retinopathy or nephropathy or neuropathy).
Exclusion criteria were: acute disease requiring hospitalization, chronic kidney disease with eGFR lower than 50 ml/min per 1.73 m^2, history of parathyroid or thyroid disease, history of sarcoidosis, or systemic steroid therapy. Skin accumulation of AGEs was determined using AGE Reader device (DiagnOptics, Groningen, The Netherlands), that measures skin autofluorescence (AF). Mean from three consecutive AF measurements was used. Serum 25(OH)D3 concentration was measured using automated immunoassay (Liaison analyser). In statistical analysis Pearson's correlation and multivariate linear regression were used.
Results
Mean 25(OH)D3 level was low and equalled 17.1(9.7) ng/ml. In 70 patients 25(OH)D3 level was lower than 20 ng/ml and in 18 patients was lower than 10 ng/ml. Serum 25(OH)D3 concentration was less decreased in women than in men (20.4(10.9) vs 14.2(7.3) ng/ml) and correlated negatively with skin AF ($r = -0.26$, $P = 0.009$). In multivariate linear regression model this association was independent from age, sex, BMI, presence of hypertension, cigarette smoking, eGFR, HbA1c value and serum LDL-cholesterol concentration (Beta: -0.29, $P = 0.006$, r^2 0.29).
Conclusion
Vitamin D deficiency is common in adults with T1DM. In this group, low serum 25(OH)D3 concentration is associated with increased skin accumulation of AGEs, independently from other parameters of metabolic control of diabetes.

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P379

Mean platelet volume reflects framingham risk score in intermediate hyperglycemia

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Background and aims
Intermediate hyperglycemia has been established to increase cardiovascular disease (CVD) risk. The increased platelet activity is believed to play a central role in pathogenesis of CVD. Mean platelet volume (MPV) and urinary

11-dehydro-thromboxane B_2 (11-dehydro-TxB_2) level have been validated as a reliable and non-invasive marker for platelet activity. The objective was to evaluate the association between these markers and CVD risk by Framingham risk score (FRS) in normal glucose tolerance (NGT) and intermediate hyperglycemia (IH).
Methods
We prospectively studied 2,145 adults who were 40–79 years of age and who underwent voluntary regular health check-ups at the Health Promotion Center of our hospital from July 2010 to June 2012. The subjects were divided into two groups with NGT and IH based on the HbA1c and fasting plasma glucose. Then these groups were subdivided into each three groups by the value of platelet activation markers to evaluate the relationship with CVD risk by FRS.
Results
The mean CVD 10-year risk by FRS increased significantly by increasing tertiles of MPV (T1, 5.03±4.85; T2, 5.30±5.41; T3, 6.12±6.11; P for trend=0.01) in IH, but not NGT. Although urinary 11-dehydro-TxB_2 excretion level was significantly higher in IH compared to NGT ($P<0.01$), the mean CVD 10-year risk by FRS did not differ between the tertiles in IH and NGT. After adjusting for risk factors associated with increasing CVD risk, upper tertile of MPV were significantly associated with CVD 10-year risk≥10% (OR 1.97 (1.34–2.89)) in IH, but not NGT.
Conclusion
MPV was positively associated with CVD risk by FRS in only IH. Therefore we propose that MPV can be a useful marker for prediction of CVD in patients with IH.

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P380

Anthropometric and biochemical parameters in older women with a history of gestational diabetes

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Introduction
Gestational diabetes mellitus (GDM) is a condition that occurs during pregnancy when the body cannot produce enough insulin to handle the effects of a growing baby and changing hormone levels. Numerous studies reported that an increased risk of GDM among women who are overweight or obese compared with lean or normal-weight women.
Methods/design
The purpose of this study is to compare anthropometric and biochemical parameters in postmenopausal women with a history of GDM and controls. Subjects were 28 overweight/obese, postmenopausal and sedentary women who had a history of GDM and 27 postmenopausal without a history of GDM as healthy postmenopausal controls.
Results and conclusion
We observed significantly higher ALB, Protprandial insulin, ANTIT and GGT levels in patient with gestational diabetes while decreased FSH, LH and Thyroglobulin levels. We could not find any differences in fasting glucose, BMI, WHR, TSH and ALT levels. This study supported that GDM is a predisposing factor for DM after menopause.

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P381

Changes of sphingolipid profiles in serum of patients with diabetes

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Ceramide (Cer) and sphingomyelin (SM) belong to a family of sphingolipids (SLs). Both SLs are mixtures of many species, differed in length and saturation of the fatty acid chain. Cer and SM are important components of the plasma membrane. In addition, Cer is a cellular second messenger, mediating apoptosis. The altered profiles of blood plasma/serum SLs were found in many pathologies. Interestingly, circulating SLs were proposed to be the early predictors of Alzheimer disease. We tested whether serum Cer and SM levels undergo changes in diabetic patients. The newly diagnosed patients were divided in two groups: those with diabetes type 1 ($n=39$) and type 2 ($n=21$), based on the presence or absence of anti-GAD antibodies. The age-matched individuals were used as controls ($n=15$). SLs were extracted from serum of the subjects and analyzed by gas-liquid chromatography. Any significant changes were observed in total Cer and SM concentrations among studied groups. Both Cer and SM were grouped into SLs containing SAFAs (saturated fatty acids), MUFAs (monounsaturated fatty acids) and PUFAs (polyunsaturated fatty acids). In all studied groups, only SM-PUFA levels significantly increased in patients with diabetes type 1. On the other hand, several Cer or SM species altered significantly in both types of diabetes. Thus, in serum of subjects with anti-GAD Abs, the significant elevations of SM-C16:0, SM-C16:1, SM-C18:1, SM-C18:2, SM-C18:3 and SM-C20:4 were noted, whereas patients without anti-GAD Abs revealed an augmentation of SM-C16:1, SM-C18:3 and Cer-C18:0 levels, and decrease of Cer-C14:0 concentration. In conclusion, patients with diabetes type 1 presented distinct pattern of SL changes in serum than those with diabetes type 2. However, the further studies are needed to determine the possible suitability of SL profiling as a diagnostic tool in diabetes.

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P382

Iranians face with the same barriers to diabetes self management as people in other parts of the world. Need for family support

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Method
One hundred and twenty-five respondents with type 1or type 2 diabetes, of both genders, were recruited from patients attending a private diabetes clinic in Karaj, Iran. They were asked to fill out the psychosocial barriers to self-care Questionnaire designed by Glasgow et al for estimating the frequency of occurrence of both environmental (e.g. time, competing demands, social pressure) and cognitive factors that interfere with diabetes self-management. Demographics and participants' latest HbA1c were also collected.
Results
General and dietary barriers were the most frequent barriers to self-care behaviours(the outstanding item amongst them was being busy with ordinary daily tasks, 28% every day and 71% at least once a month), followed by barriers to exercise. Medication-taking barriers were less frequent, and barriers to glucose testing were reported least often. There were significant correlations between level of HbA1c with both dietary barriers and barriers to medication-taking. The results showed some similarity to those of Glasgow *et al.* (1989a and 1989b), however, in contrast with our results, glucose testing barriers were less frequent and barriers to medication-taking were reported least often.
Conclusions
Among Iranian population in the current study the most frequent obstacles to diabetes self-care were general barriers followed closely by barriers to diet and exercise. These findings point to the importance of family education and support for successful diabetes treatment.

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P383

Low apelin levels are associated with a marked increase in risk for development of the gestational diabetes mellitus

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Introduction
Apelin is an adipokine which plays a role in the regulation of glucose homeostasis. The relationship between apelin serum concentration and dysmetabolic conditions such as type 2 diabetes (T2D) is still controversial. The aim of our study was to investigate the association of apelin with gestational diabetes mellitus (GDM).

Design and methods
This study was designed as a cross-sectional research that consecutively recruited subjects with GDM ($n=38$), without GDM pregnant ($n=41$), and non-pregnant healthy women ($n=39$).
Fasting blood glucose (FBG), serum apelin, insulin and lipids were measured. BMI and HOMA-IR were calculated for all subjects.
Results
Serum apelin levels (GDM = 1.99 ± 1.36 μg/ml, non-GDM pregnant = 2.95 ± 1.36 μg/ml, non-pregnant women = 2.62 ± 1.67 μg/ml) were significantly lower ($P=0.017$), HOMA-IR ($P=0.024$) and BMI ($P<0.001$) were significantly higher in the GDM group compared with both the non-GDM and the non-pregnant women.
Serum apelin levels were found to be negatively correlated with FBG ($r=-0.236$, $P=0.010$), OGTT 1 h glucose ($r=-0.346$, $P=0.002$) & 2 h glucose ($r=-0.248$, $P=0.028$), A_{1C} ($r=-0.209$, $P=0.023$), HOMA-IR ($r=-0.360$, $P<0.001$) and BMI ($r=-0.299$, $P=0.001$).
Conclusions
Serum apelin levels were significantly lower in the GDM group as compared with both the non-GDM pregnant and the non-pregnant healthy women. Serum apelin levels were negatively correlated with FBG, OGTT 1 & 2 h glucose, A_{1C}, HOMA-IR and BMI. Furthermore; the outcome of the logistic regression analysis showed that low apelin levels alone, pose a risk for developing GDM independent of other variables (Odds ratio = 0.616, 95% CI = 0.406–0.935, $P=0.023$). To clarify whether it may be an early diagnostic or at least an alarming marker of GDM, prospective studies can be planned in pregnant women to measure apelin levels periodically beginning at the first trimester and continuing until term.
Keywords
GDM, Apelin, HOMA-IR, A_{1C}
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P384

Translating the A1C assay into estimated average fasting glucose values: Data from the 2011 Korea National Health and Nutrition Examination Survey V

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Aim
An international expert committee, after considering data on association of HbA1c and retinopathy, recommended that diabetes be diagnosed when HbA1c is more than 48 mmol/mol (>6.5%), provided this assay is done in a standardized laboratory. However, the performance of HbA1c in detecting diabetes in the Korean population remains unknown. The purpose of this study was to evaluate the efficiency of HbA1c in diagnosing diabetes and to identify the optimal threshold in the adult Korean population by using high performance liquid chromatography.
Methods
We analyzed data for an initial total of 8,518 men and women, 6,066 persons (2,677 men and 3,389 women), with HbA1c and fasting glucose data and without diabetes medication from 2011 KNHANES. We investigated the association in fasting blood glucose and HbA1c and the difference in the diagnosis of diabetes, based on the health interview and health examination data of KNHANES V. The threshold for the diagnosis of diabetes was 126 mg/dl and more by fasting blood glucose level and 6.5% or higher by hemoglobin A1c level.
Results
Proportions of persons with diabetes person (suggested definition of fasting blood glucose and HbA1c) were 2.5 and 3.3%, respectively, in this study populations. Percentages of persons with diabetes by fasting glucose but not HbA1c were 0.9% and percentages of persons with diabetes by HbA1c but not fasting glucose were 1.7%. The Pearson correlation coefficient (r) was 0.83. The change in HbA1c per increase of 10 mg/dl fasting blood glucose was 0.25% which was similar previous result but fasting blood glucose 101 mg/dl predicted HbA1c 6.5%.
Conclusions
An HbA1c threshold of 6.5% was highly specific for detecting undiagnosed diabetes in Korean adults and had sensitivity similar to that of using a fasting plasma glucose threshold of 126 mg/dl. This optimal HbA1c threshold may be suitable as a diagnostic criterion for diabetes in Korean adults when fasting plasma glucose is not available.
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P385

Presence of erythrocytosis in a patient with concomitant type 1 diabetes mellitus and Gitelman syndrome

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İntroduction
Gitelman syndrome is characterized with hypokalemia, hypomagnesemia, hypocalciuria, metabolic alkalosis and neurological symptoms like muscle weakness. The association of GS and type 1 diabetes is rare, only described in a few case reports. We report a patient with unusual combination of Gitelman syndrome, Type 1 Diabetes Mellitus whose presentation was erytrocytosis.
Case
A 26-year old male was diagnosed as Gitelman's syndrome 5 years ago. After 2 years of his diagnosis he was diagnosed as type 1 diabetes. He was on insulin therapy. 3 years after his diagnosis of type 1 diabetes he was referred to our hospital with poor glycemic control and headache. Further hematological and biochemical work-up showed; increased hemoglobin (18.9 g/dl (13.6–17.2 g/dl)), increased hematocrit (54.8% (39.5–50.3%)), hyperglycemia (246 mg/dl (75–99 mg/dl)), hypokalemia (2.62 mmol/l (3.5–5 mmol/l)), hypochloremia (92 mmol/l (96–110 mmol/l)), elevated renin (592 pg/ml (0.2–27.8 pg/ml)), slightly elevated aldosterone (525 pg/ml (30–313 pg/ml)). GFR was 109 ml/min (Cockgroft-Gault formula). Erythropoietin (EPO) level was 23.4 mU/ml (3.7–31.5 mU/ml) and JAK2 V617F gene mutation was negative. A bone marrow aspiration biopsy revealed a hypercellular marrow with increased erythroid precursors, megacaryocytes and granulocytes. His chest radiography, abdominal ultrasound, echocardiography were normal.
Discussion
Concomitant presence of GS with a type 1 diabetic patient complicated the treatment of glycemia because of hypokalemia. Both type 1 diabetes and Gitelman syndrome have effects on kidneys and the primary site of erythropoietin production is kidney. There must be a 40–45% reduction in the plasma volume to explain the higher hemoglobin concentration without a rise in the red blood cell mass. In our case, GFR was in normal range and there was no evidence of hypovolemia or proteinuria that might cause renin angiotensin axis overstimulation. We excluded cronic myeloid neoplasm. In conclusion, our patient besides having Gitelman syndrome and type 1 diabetes was complicated with idiopathic erythrocytosis, all having deleterious effects on hemodynamic features of the patient.
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P386

Incidence of type 1 diabetes mellitus over 21 consecutive years among 15–39-year aged Lithuanian population

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Objective
To document the incidence of type 1 diabetes mellitus in Lithuanian 15–39 years of age population from 1991 to 2012.
Research design and methods
A specifically developed contact system with all endocrinologists and diabetologists and general practitioners involved in the diabetes care covering 100% of the Lithuanian population aged 15–39, was the initial data source. Annual reports from regional family physicians, endocrinologist's and diabetologists, statistical note-marks of diabetic patients who visited Medical Units, death certificates and patients' lists from Diabetes Societies remained as secondary independent sources for case ascertainment.
Results
The total of 1,511 new cases (789 males and 722 females) of type 1 diabetes mellitus were recorded among the population 15–39-year of age during the period 1 January 1991–31 December 2012. The cumulative incidence density per year was 8.40/100,000 (95% Poisson distribution confidence interval 8.06–8.75) and was slightly higher among males (10.98/100,000, 95% CI 10.44–11.54) than among females (5.79/100,000, 95% CI 5.40–6.21), $P<0.0001$. Age standardized and age adjusted overall incidence rates for males and females were 10.99 and 5.81, respectively. Male/female ratio was 1.92. Results of the linear regression models showed that the incidence density of type 1 diabetes mellitus in 15–39-year age group had very slow tendency to decrease.
Conclusions
The results suggest that the incidence data of type 1 diabetes mellitus in Lithuania in 15–39-year-aged group is lower than in other countries of Baltic Sea region. The data contributes to the knowledge of the incidence of type 1 diabetes mellitus in Eastern Baltic countries, an area that until now has been lacking epidemiological data on diabetes among 15–39-year aged population.
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P387

The *HLA-A*33* haplotype enhances the risk of type 1 diabetesin ndividuals with HLA-DR3$^+$ or DR9$^+$ haplotype

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Background
To investigate the typing for HLA-I in Chinese patients with type 1 diabetes (T1D) as a complement screening for HLA-II.
Methods
A total of 212 T1D patients and 200 healthy controls were enrolled. The genetic polymorphisms of *HLA-I* and *II* were examined with a high-resolution polymerase chain reaction-sequence-based typing method.
Results
The novel haplotype, *A*33:03-B*58:01-C*03:02(A33)*, was associated with T1D ($P<0.001$, OR 3.2(1.738–5.843)). The A33 haplotype significantly enhanced the risk of T1D with specific *HLA-DR/DQ* haplotypes (DR3, OR 5.1(2.40–10.78)), $P<0.001$; DR9, OR 13.0(1.69–100.32), $P=0.004$). Compared to *A33-DR3*-negative carriers, *A33-DR3*-positive carriers had significantly lower percentages of CD3$^+$CD4$^+$T cells (42.5±7.72 *vs* 37.0±8.35%, $P=0.011$), higher percentages of CD3$^+$CD8$^+$T cells (27.4±7.09 *vs* 32.8±5.98%, $P=0.003$), CD45RA$^+$CD62L$^+$T cells (43.2±14.15 *vs* 50.5±9.75%, $P=0.042$) and TCRα/β T cells (70.0±7.00 *vs* 73.6±6.25%, $P=0.037$), and lower CD4/CD8 ratios (1.71±0.75 *vs* 1.16±0.35, $P<0.001$).
Conclusion
A novel haplotype A33 was found with enhanced predisposition to T1D for DR3 or DR9 carriers. *A33-DR3* was associated with a striking reduction in the helper-to-cytotoxic cell ratio and preferential stimulation of 'naive' T cell and regulatory T cell. The typing for HLA-I and its immunogenic effects are important for more accurate HLA-II haplotype risk prediction and etiologic research in T1D patients.

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P388

What is the contribution of MODY gene polymorphisms in the development of gestational diabetes mellitus?

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Objective
Gestational diabetes mellitus (GDM) is the consequence of increased insulin resistance during pregnancy in predisposed individuals who already have impaired insulin secretion due to beta-cell dysfunction as in maturity onset diabetes of young (MODY) cases. Here we aimed to document the association between MODY subtypes and GDM to understand the pathogenesis of GD.
Design
Matched, case-control study.
Method
Ninety-three patients with the diagnosis of GDM according to the diagnostic criteria of 2011 ADA and 89 healthy pregnant non-diabetic subjects participated in this study. Patients with T1DM or T2DM diagnosis before pregnancy or with organ failure were excluded. Peripheric blood samples were obtained from all the participants to study the genetic polymorphims of *GCK* (rs1799884), *HNF1A* (rs1169288) and *HNF4A* (rs2144908) genes. The association between GDM and gene polymorphisms were examined.
Results
HNF1A (rs1169288) gene polymorphism was positively correlated with GDM which was statistically significant ($P=0.038$). Although *IGF2BP2* (rs1470579) and *GCK* (rs1799884) gene polymorhisms were more frequent in GDM group, this association was not statistically significant. There was no association between *GDM* and *HNF1A* (rs1169288) gene polymorphism. Besides these, as the number of the risk alleles of the three genes, included in our study, increasing; the risk of GDM increased as well ($P=0.012$). In addition to this, individuals with the risk allels of *GCK* gene have had higher HbA1c and post-OGTT glucose levels ($P=0.028$ and $P=0.010$ respectively).
Conclusions
The risk of GDM is related to the additive effect of these three genes (*GCK* (rs1799884), *HNF1A* (rs1169288) and *HNF1A* (rs1169288)) rather than a single gene effect which was firstly described here in our study.

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P389

Characterization of severe hypoglycemia episodes evaluated in the emergency department of a central hospital

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Introduction
Hypoglycemia is a major limiting factor in intensive glucose control in diabetes mellitus. Its incidence has been increasing with the demand for intensive therapy for the prevention of the diabetic chronic complications. There are few studies in our country regarding the evaluation of hypoglycemia in the emergency room (ER).
Objective
To characterize severe hypoglycemia episodes and patient features in individuals admitted to the ER.
Methods
We obtained data regarding hypoglycemia episodes evaluated in the ER of our hospital between 1st January and 31st March 2010. We recorded the demographic and clinical data of the patients and destination after discharge.
Results
We recorded 61 episodes of severe hypoglycemia – 0.16% of total ER episodes. Mean glycemia at admission was 103.3±80.52 mg/dl0 (excluding 1 episode with *Low*). It is of notice that in 30 episodes (49.2%), the patients arrived to the ER hypoglycemic (1 *Low*; average 44.0±16.38 mg/dl). Of 59 patients evaluated, 28 (47.5%) were male. The mean age of the patients was 68.0±15.26 years. Five (8.5%) patients had type 1 diabetes mellitus, 48 (81.4%) had type 2 diabetes mellitus and 6 (10.2%) had other types of diabetes. Regarding the type of diabetes therapy, 21 (35.2%) patients were only oral medication treated, 30 (50.8%) were only insulin treated and 8 (13.6%) were treated with oral agents and insulin association. Nineteen (31.1%) patients were admitted to the ward. Of the total of patients, 17 died, on average, 13 months after the episode.
Conclusion
Among the patients evaluated for severe hypoglycemia in the ER, there is a higher prevalence of type 2 diabetics, older age and insulin treated individuals. This study reveals serious deficiencies in the evaluation and treatment of severe hypoglycemia in the pre-hospital emergency care. It is essential to improve the evaluation and treatment of severe hypoglycemia in the latter setting.

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P390

Characterization of the episodes of severe hypoglycemia evaluated by a pre-hospital care unit of a reference hospital

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Introduction
Severe hypoglycemia is defined as an episode that requires the assistance of another person in order to correct it. Most of the costs associated with hypoglycemia in diabetes mellitus patients are the result of severe episodes,

when treated by health care professionals. In our country there are few studies regarding the epidemiology of episodes of hypoglycemia evaluated in the pre-hospital care setting.
Methods
We retrieved all episodes of hypoglycemia evaluated by a pre-hospital care unit of a reference hospital between 1st January and 31st March 2010, and recorded demographic data and the medication used.
Results
We recorded 37 episodes of severe hypoglycemia (4.7% of a total 793 emergency episodes). Thirteen episodes (35.1%) were nocturnal. At arrival, the mean Glasgow Coma Scale was 8.0±4.71 and the mean capillary glucose was 32.0±14.96 mg/dl (1.8±0.83 mmol/l). The mean age of patients was 60.7±18.36 years (minimum 27 – maximum 84 years) and 10 (27.8%) patients were male. Of 31 patients with available information regarding type of diabetes, 11 (35.5%) had type 1 diabetes and 20 (64.5%) had type 2 diabetes. Of 21 patients with data on diabetes treatment, 21 (65.6%) were treated with insulin, 6 (18.8%) with oral medication and 5 (15.6%) with combined insulin and oral medication therapy. Of 11 patients treated with oral agents, 6 (54.5%) were using sulphonylureas. Seventeen episodes (45.9%) resulted in the transportation of the patient to the emergency room, 14 of which involved type 2 diabetics.
Conclusions
Severe hypoglycemia is a frequent cause of emergency calls and evaluation by a pre-hospital care unit. It occurs in type 1 and type 2 diabetics alike, as well as individuals of all age groups. Less than half of episodes result in transportation to an emergency department and type 1 diabetics are more likely to maintain an ambulatory treatment plan.

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P391

Vitamin D, insulin dependency and BMI in type 1 diabetes

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Type 1 diabetes mellitus (T1D) is caused by a process of altered humoral and cellular immunity, resulting in the destruction of insulin-producing cells. VD(25(OH)D^3) insufficiency is implied as risk factor for T1D, while VD substitution in infantry is associated with a reduced T1D incidence. In T1D daily insulin injection is required for a stable glucose homeostasis and insulin demand rises by a higher Body Mass Index (BMI). Today there are no studies investigating the relations between endogenous VD production and insulin demand in T1D.
Methods
Twenty-nine T1D patients were examined for insulin demand (Carbohydrate Factor-IU/12 g carbohydrates (CF); basal insulin-IU/d), BMI (kg/m^2) and VD (ng/ml). For our study we used the Mann-Whitney *U* and Spearman's tests.
Results
The median VD was 18.7. Six patients (20.68%) were VD deficient (<10), 16 (55.17%) insufficient (<20) and 13 (44.82%) sufficient (>20). Interestingly, CF in the afternoon was significantly higher in the group with VD<20 than in the group>20(2 *vs* 1.25; $P=0.03$). CF in the morning and basal insulin exhibited a trend to be higher in the group with VD<20 compared to the group with VD>20(2 *vs* 1.3 and 18.1 *vs* 17.65; $P=0.09$ and $P=0.15$ respectively.). Furthermore the median BMI was 24.8, so we divided our patients in 2 groups (BMI<24.8> respectively.). The VD levels did not differ between the group ($P=0.96$). The basal insulin demand was significantly higher in the group with a BMI>24.8 compared to the group with a BMI<24.8(15 *vs* 21.4; $P=0.01$). A significant negative correlation between CF in the morning, basal insulin demand and VD levels was proven in the group with BMI>24.8 ($P<0.05$, rho=−0.57 respectively.), whereas in the group with a BMI<24.8 there were no significant correlations.
Conclusion
In our study lower VD levels were associated with a higher insulin demand; in preadipose T1D patients there was a significant negative correlation. Interesting would be to study whether a VD substitution could decrease insulin demand as an option for an adjunctive therapy of T1D.

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P392

Resistin mRNA expression in fat and placental tissue of patients with gestational diabetes

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Introduction
Resistin is a cysteine–rich adipokine that was originally described as a molecular link between obesity and insulin resistance. Our previous study showed higher serum resistin levels in patients with gestational diabetes mellitus (GDM) in comparison with healthy pregnant women however conflicting results have been reported by other authors. Therefore in the present study we investigated whether there were significant differences in resistin mRNA expression in adipose and placental tissue obtained from pregnant women with normal glucose tolerance (NGT) and GDM.
Methods
Resistin, adiponectin and Interleukin-6 (IL-6) mRNA expression was measured in paired samples of subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT) and placental tissue from 21 patients with GDM and 21 healthy pregnant controls, using quantitative RT-PCR.
Results
The patients with GDM had significantly higher resistin mRNA expression in placental tissue ($P=0.03$) and lower adiponectin mRNA expression in VAT ($P=0.039$), whereas IL-6 mRNA expression did not differ markedly between the groups studied. Resistin mRNA expression in SAT and VAT correlated positively with IL-6 mRNA ($R=0.54$, $P=0.0004$ and $R=0.44$, $P=0.009$ respectively) and negatively with adiponectin mRNA expression ($R=-0.35$, $P=0.03$ and $R=-0.39$, $P=0.02$ respectively), whereas resistin mRNA expression in placental tissue was positively associated with IL-6 mRNA ($R=0.68$, $P=0.00001$), HOMA-IR ($R=0.42$, $P=0.03$) and newborn weight ($R=0.40$, $P=0.02$).
Conclusions
Our results suggest that elevated resistin expression in placental tissue might be associated with insulin resistance and low grade inflammation in women with GDM.

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P393

Clinic blood pressure shows low sensitivity to detect alterations in ambulatory blood pressure monitoring in patients with type 1 diabetes

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Objectives
To evaluate the validity as diagnostic test of isolated blood pressure measurement compared to 24 h ambulatory blood pressure monitoring (ABPM) in a group of clinically normotensive patients with type 1 diabetes (TDM1).
Methods
Cross-sectional study including 85 normotensive and normoalbuminuric patients with TDM1. Media of two blood pressure measures by conventional technique and results of the 24 h blood pressure monitoring (SPACELABS 90217) were compared. Altered ABPM was considered when: 1) Mean systolic pressure (sBP) was greater than 130 mmHg in the 24 h and daytime periods and greater than 120 mmHg in the night-time period and/or mean diastolic pressure (dBP) greater than 80 or 70 mmHg in the same periods respectively, and/or 2) More than 50% of the readings were higher than the defined previous criteria, and/or 3) Nocturnal fall in either sBP or dBP was lower than 10% (non-dippers).
Results
Eighty-five patients, 55% women, aged 27.9±6.1 years and 12.3±6.5 years of disease evolution. The maximum sensitivity of the conventional technique (systolic and diastolic records) to detect any ABPM disturbances was less than 75%, and almost zero for the presence of a non-dipper pattern. However, the specificity was higher, almost always above 85%.

Conclusions
Isolated blood pressure (systolic or diastolic) as a diagnostic test showed high specificity but low sensitivity, so this measure may not be suitable as a screening method for hypertension in normotensive and normoalbuminuric patients with type 1 diabetes. Criteria to perform ABPM in this patients should be defined to detect subclinical blood pressure alterations and to assess the convenience of drug treatment.

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Increased prevalence of hepatocellular carcinoma in patients with cirrhosis and insulin resistance candidate to liver transplantation

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Introduction
Hepatocellular carcinoma (HCC) is the first cause of death in patients with cirrhosis, with an incidence of 3–5% per year and a survival of 0–10% 5 years after the diagnosis. Major risk factors for HCC are HCV, HBV infection and alcohol, while a specific cause is not identifiable in 5–30% of cases. Several studies have shown a strong association between metabolic syndrome (MS), characterized by insulin-resistance (IR) and central obesity, and HCC; In patients with liver cirrhosis, however, diagnosis of MS can be very difficult because of the presence of several confounders as ascites and edema, which invalidate the use of BMI and waist circumference, the use of diuretics and beta-blockers, which hide the presence of hypertension, altered glucose and cholesterol metabolism. For this reasons the availability of mathematical indices is fundamental to recognize insulin-resistant people in this population.
Aim of the study
Evaluate, in cirrhotic patients in waiting list for liver transplantation, the presence of insulin resistance and its association with increased risk of HCC.
Materials and methods
One hundred and four patients 33M/71F, age 53 ± 9, with liver cirrhosis, 30 of them affected by HCC. They underwent an anthropometric and metabolic evaluation and an OGTT. Insulin resistance was assessed with HOMA, OGIS-2 h and MATSUDA index. Regarding to HOMA, we used a cut off of 3 to identify insulin-resistant patients.
Results
Prevalence of HCC was significantly higher in cirrhotic patients with insulin-resistance assessed by HOMA, *vs* cirrhotic patients without insulin-resistance (39% *vs* 16%, $P < 0.05$). In our population there were no significant differences in OGIS and MATSUDA indices.
Conclusions
In patients with end-stage liver disease, HOMA, a reliable index to identify insulin-resistant patients, allows to characterize a class of patients at highest risk of developing HCC.

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Alterations in ambulatory blood pressure monitoring are associated to proinflammatory cytokines in patients with type 1 diabetes

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Objectives
To evaluate the prevalence of blood pressure alterations with ambulatory blood pressure monitoring (ABPM) and its association with proinflammatory cytokines (IL-6 and VEGFα) in normotensive and normoalbuminuric patients with type 1 diabetes (TDM1).
Patients and methods
Cross-sectional study including normotensive and normoalbuminuric patients with TDM1. Altered ABPM was considered when: 1) Mean systolic pressure (sBP) was greater than 130 mmHg in the 24 h and daytime periods and greater than 120 mmHg in the night-time period and/or mean diastolic pressure (dBP) greater than 80 or 70 mmHg in the same periods respectively, and/or 2) More than 50% of the readings were higher than the defined previous criteria, and/or 3) Nocturnal fall in either sBP or dBP was lower than 10% (non-dippers). Serum cytokines levels, including IL-6 and VEGF-α, were measured using Procarta® Immunoassays (Affymetrix).
Results
Eighty-five type 1 diabetic patients (55% women) aged 27.9 ± 6.1 years with a disease duration of 12.3 ± 6.5 years. 32% presented mean sBP or dBP altered during daytime, 32% more than 50% of pathological readings during daytime and 41.6% (*n*:36) were non-dippers. Significant correlation was detected between IL-6 and 24 h dBP (*r*: 0.17, *P*: 0.02), 50% of 24 h dBP high (*r*: 0.15, *P*: 0.04) and daytime dBP (*r*: 0.16, *P*: 0.03). There was also a statistically significant correlation between VEGFα and 24 h sBP (*r*: 0.19, *P*: 0.006), 24 h dBP (*r*: 0.24, *P*: 0.002), 50% of 24 h sBP (*r*: 0.2, *P*: 0.009), 50% of 24 h dBP (*r*: 0.21, *P*: 0.06) and daytime sBP (*r*: 0.22, *P*: 0.005). Mean values of both cytokines did not differ between dipper and non dipper patients.
Conclusion
Altered ABPM is prevalent in normotensive and normoalbuminuric patients with type 1 diabetes and related to proinflammatory cytokines. Prospective studies should evaluate if proinflammatory cytokines play a role in hypertension development in this type of patients.

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Vitamin D and diabetes mellitus type 2

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Vitamin D deficiency has been observed in diabetes mellitus type 2 patients. It has been found to be related to poor glycemic control in diabetes mellitus type 2 patients as well as in patients with gestational diabetes. The administration of vitamin D in diabetes mellitus type 2 patients with vitamin D deficiency has been found to have conflicting results on blood glucose control. The aim was to assess the effect of vitamin D administration in diabetes mellitus type 2 patients with vitamin D deficiency on blood glucose control.In a group of 20 diabetes mellitus type 2 patients with vitamin D deficiency vitamin D was administered along with oral hypoglycemic agents. $25(OH)D_3$ and glycosylated hemoglobin levels were measured at the beginning of the study and 3 months later. Patients were on treatment with oral hypoglycemic agents. Cholecalciferol was administered orally at a dose of 1,200 IU daily for a period of 3 months. At the beginning of the study diabetes mellitus type 2 patients were found to have vitamin D deficiency, $25(OH)D_3$ levels being 18.6 ± 0.86 ng/ml (mean ± S.E.M), glycosylated hemoglobin levels being $7.1 \pm 0.15\%$. After the administration of cholecalciferol for a period of 3 months glycosylated hemoglobin levels decreased to $6.56 \pm 0.19\%$ ($P < 0.05$, Student's *t* test). Vitamin D supplementation in diabetes mellitus type 2 patients on oral hypoglycemic agents may contribute to better blood glucose control. These results are in accordance with the known effect of vitamin D on insulin secretion as well as on insulin sensitivity. However, as the study involved diabetes mellitus type 2 patients the effect of better adherence to dietary restrictions or improved compliance to the oral hypoglycemic treatment on blood glucose control cannot be excluded.

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Features of patients with LADA in a Diabetes Unit

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Introduction
Latent Autoimmune Diabetes in Adults (LADA) is a form of diabetes which is underdiagnosed and appears to have characteristics of both type 1 (autoimmune in

nature) and type 2 diabetes (adult age at onset and initial response to oral hypoglycemic agents).
Objective
To study features of patients with LADA diagnosed and treated in our clinic.
Material and methods
Retrospective study of patients attended in our clinic in last 2 years.
Results
We obtained data about 27 patients with LADA.
Mean age
61.8 years, men age at onset: 47.55 (30–69) years, 55.6% women. 50% were obese (mean weight 69.66 kg), 75% were hypertensive and 75% had dyslipaemia. Mean HbA1c at diagnosis: 9.8%, mean Peptide C at diagnosis: 0.68. 66.7% had positive IA2 and 77.8% AntiGAD. Mean Insulin independence period: 60.4 ± 46.5 months. Metabolic control: current HbA1c: 7.93%, number of hyperglycemias (>250) in a month: 2.5, number of hypoglycemias in a month: 2.1 and number of severe hypoglycemias in a year: 0.88. Current treatment: 55.6% are treated with basal and rapid insulin, 22.2% with OADs, basal and rapid insulin and 22.2% only with OADs and basal insulin. Complications: 22.2% have retinopathy, 11.1% have nephropathy, 0% neuropathy and 33% cardiovascular disease.
Conclusion
Our patients have a long time of insulin independence maintaining adequate control with OADS.
Diagnosis of LADA represents a challenge for the physician and the optimal treatment is not established.

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P398

Paper of oxidative stress and placenta on the development of gestational diabetes mellitus

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The relationship between gestational diabetes mellitus (GDM) and oxidative stress is not well known and the effect of oxidative stress in GDM placenta and the impact that could have on perinatal morbidity and risk of future complications is also yet to be elucidated. The aim of the study was to evaluate the relationships between maternal and placental tissue levels of markers of oxidative stress and antioxidants in women with GDM, which potentially may have considerable clinical implications in the pathogenesis and/or the evolution of GDM.Pregnant women ($n=78$; 53 with GDM, 25 controls), between the 24th and 29th week of gestation were enrolled. Both groups were analyzed for demographic data, perinatal and obstetrics results and the levels of the markers oxidative stress and antioxidants status were measured. Seven placenta GDM and seven normal placenta were studied. In the univariate analysis control versus patient results were: pre-gestational BMI 23.31 ± 4.2 *vs* 27.13 ± 4.6 kg/m^2 ($P=0.001$); 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 *vs* 3.14 ± 1.55 µmol/mg ($P=0.001$); catalase 3.23 ± 1.41 *vs* 2.52 ± 1.3 nmol/min per ml ($P=0.03$); superoxide dismutase (SOD) 0.11 ± 0.04 *vs* 0.08 ± 0.01 U/ml ($P=0.0003$); glutathione peroxidase (GPX) 0.03 ± 0.006 *vs* 0.025 ± 0.006 nmol/-min per ml ($P=0.01$); glutathione reductase (GSH) 0.004 ± 0.002 *vs* 0.004 ± 0.004 nmol/min per ml ($P=0.9$)); glutathione transferase (GST) 0.0025 ± 0.0012 *vs* 0.0027 ± 0.00017 nmol/min per ml ($P=0.7$). Multivariate analysis showed catalase might have a protective effect and LPO seems to be a risk factor for GDM development. In GDM placenta levels catalase ($n=0.05$), SOD ($n=0.03$) and GPx ($n=0.04$) were significantly increased. These data suggest an increase in oxidative stress and a decrease in antioxidative defence in women with GDM and, as such, may have considerable clinical implications in the pathogenesis and/or the course of the pregnancy in these patients.

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Evaluation of the approach to diabetic patients before the first admission to diabetologist: Is there a room for the improvement?

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Introduction
Diabetes mellitus (DM) is a chronic disease that can be largely managed in the primary care system.
Aim
We analysed medical records of diabetic patients (pts) treated in Center for diabetes in our institution, during 1 year, determining the quality of care.
Material and methods
The search was focused on pts at first admission to the diabetologist. Analysis included demographic and clinical characteristics of pts, metabolic control, prevalence of diabetic complications and cardiovascular risk factors. All data related to every patient were found searching the central medical database. The analysis covered the last 3 years, with all available laboratory results, hospitalizations and specialist exams.
Results
Between 4,792 medical records, 236 patients were examined for the first time in outpatient clinic, and 156 pts during hospitalization. Of 236 ambulatory pts, 100 were newly diagnosed (1), and 136 were known DM pts (2). In the first subgroup (1) HbA1c measurements were found in 39% of pts, renal parameters in 69%, hepatal function was determined in 72% of pts, microalbuminuria in 3% and fundoscopy in 13% of pts. Thirty one percent of pts were later diagnosed. In the second subgroup (2) HbA1c was measured in 69% of pts, renal parameters in 85%, hepatal function was determined in 77% of pts, microalbuminuria in 7% and fundoscopy in 13% of pts; 7% of pts were diagnosed later. Only 12% of pts in subgroup (1) had an initial therapy prescribed in primary health care.
Conclusions
The quality of primary care of diabetic patients requires improvement. Evaluation of chronic complication, laboratory exams, timely diagnosis of DM, initiation of the therapy should be more frequent and regular, following the existing guidelines of care of DM patients.

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P400

Impact of Impaired Fasting Glucose on Blood Pressure and Vascular Risk Profile of Normotensives and Untreated Hypertensive Subjects

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Objective
To evaluate possible differences in 24 hours blood pressure (BP) and vascular risk profile (VRP) of normotensive (NT) and untreated hypertensive (UHT) patients with normoglycemia (NG) or Impaired Fasting Glucose (IFG).
Design and methods
From 9.812 nondiabetic subjects taken from the Spanish ABPM (Ambulatory Blood Pressure Monitoring) Registry, we compared 24-h BP and VRP differences between patients with NG [*n*-6,875 (43.3% NT and 56.7% UHT)] and those with IFG [*n*-2,937 (39.9% NT and 60.1% UHT (mean diagnosis:1.5 ± 1 years)]. All patients underwent 24-h ABPM, and, after clinical and biochemical study, their vascular risk was stratified according to 2003 ESH Guidelines.
Results
Anthropometric differences between NG/IFG subjects: mean age 51/54 years, males 43.5/46.9%, BMI 27.5/29 kg/m^2, waist circumference males 97/101, females 90/95 cm (all $P<0.001$). Associated vascular risk factors (%): obesity 45.7/48.3, central obesity 35.3/46.2, dyslipidaemia 29.8/45.7, smoking 17.6/19.5. Target organ damage: left ventricular hypertrophy 1.6/2.2, albumin/creatinine ratio >30 mg/g 6.6/8.4, carotid atherosclerosis 0.7/1.2 (all $P<0.001$). Associated clinical diseases NG/IFG subjects: 8/9.9, high plus very high cardiovascular risk 22.1/31%. Mean ABPM values (mmHg): no significant differences between any diastolic BP. Mean Systolic BP (NG/IFG subjects): 24 hours 127.8/129.8; Daytime 131.7/134.5, Nighttime 116.8/118.7, Non Dipper pattern 30.2/42.5% (all values $P<0.001$ for IFG patients).
Conclusions
Normotensive and newly untreated hypertensive with IFG have significantly higher levels of systolic BP, percentage of non-dipper pattern as well as a worse CV risk profile than normoglycemic subjects. Therefore, IFG could be considered as an independent vascular risk factor when stratifying NT and UHT individuals.

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In human retina the A allele of the −866G/A polymorphism in the UCP2 gene is associated with increased *UCP2* protein concentrations

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Introduction
Uncoupling protein 2 (UCP2) is a mitochondrial transporter present in the inner membrane of mitochondria, and it uncouples substrate oxidation from ATP synthesis, thereby dissipating the membrane potential energy and consequently decreasing ATP production by mitochondrial respiratory chain. As a consequence of the uncoupling, UCP2 decreases reactive oxygen species (ROS) formation by mitochondria. ROS overproduction is related to diabetic retinopathy (DR), a chronic complication of diabetes mellitus (DM). Recently, our group reported that the −866A/55Val/Ins haplotype (−866G/A, Ala55Val and Ins/Del polymorphisms) of the UCP2 gene was associated with risk for DR in patients with type 1 or type 2 DM. Afterwards, we showed that this haplotype influences UCP2 mRNA expression in human retina samples.
Objective
To evaluate whether the UCP2 −866A/55Val/Ins haplotype influences the amounts of UCP2 protein in human retina.
Methods
The sample was constituted by 84 healthy cadaveric cornea donors from two hospitals from Porto Alegre, Brazil. Genotyping of the −866G/A, Ala55Val and Ins/Del polymorphisms were performed by Real-time PCR using TaqMan probes. UCP2 protein distributions and intensities were determined by immunohistochemistry in formalin-fixed, paraffin-embedded retina sections, using an anti-UCP2 rabbit polyclonal antibody. Ten fields of each slide were photographed, and the intensity of UCP2 immunostaining was analyzed by two independent researchers using the Image ProPlus version 4.5 program.
Results
UCP2 immunoreactivity was not exclusive to a specific retina cell layer. The concentration of UCP2 protein in retina did not differ significantly between 28 −866A/55Val/Ins haplotype carriers and 30 WT haplotype carriers (27.1 ± 15.6 vs 20.2 ± 13.1 pixels; $P = 0.064$). However, when we analyzed each polymorphism individually, we observed that A allele carriers of the −866G/A polymorphism showed increased UCP2 levels as compared to the G/G genotype (27.9 ± 20.9 vs 20.1 ± 13.1 pixels; $P = 0.027$).
Conclusion
The −866G/A polymorphism in the promoter region of the UCP2 gene seems to be associated with increased UCP2 protein concentrations in human retina, which may explain the reported association between the −866G/55Val/Ins haplotype and risk for DR. We hypothesized that in a glucotoxicity environment, as occurring in the diabetic milieu, the A allele would be a marker of excessive ROS production, which is the actual risk factor for DR.

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P402

Association of the *UCP* polymorphisms with susceptibility to obesity: case–control study and meta-analysis

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Introduction
Some studies have reported associations between five uncoupling protein (UCP) 1–3 polymorphisms and obesity. This paper describes a case–control study and a meta-analysis conducted to determine if the following polymorphisms are associated with obesity: −3826A/G (*UCP1*); −866G/A, Ala55Val and Ins/Del (*UCP2*) and −55C/T (*UCP3*).
Methods
The case–control study enrolled 282 obese and 483 non-obese patients with type two diabetes mellitus. A literature search was conducted in order to identify all studies that investigated associations between *UCP1–3* polymorphisms and obesity. Pooled odds ratios (OR) were calculated for allele contrast, recessive, dominant and additive inheritance models.
Results
In the case–control study the frequencies of the *UCP* polymorphisms did not differ between obese and non-obese groups ($P > 0.05$). Forty-seven studies were eligible for inclusion in the meta-analyses. Meta-analysis results showed that the *UCP2* −866G/A and *UCP3* −55C/T polymorphisms were associated with protection for obesity in Europeans (−866G/A: OR = 0.89 (95% CI 0.82-0.97); −55C/T: OR = 0.88 (95% CI 0.80-0.97)) assuming dominant and co-dominant inheritance models respectively. In contrast, the *UCP2* Ala55val polymorphism was associated with risk for obesity in Asians (OR = 1.61 (95% CI 1.13-2.30)) in the recessive model, whereas the *UCP2* Ins/Del polymorphism was associated with risk for obesity mainly in Europeans under an allele contrast model (OR = 1.19 (95% CI 1.00-1.42)). No significant association was observed between the *UCP1* −3826A/G polymorphism and obesity.
Conclusions
In our case–control study we were not able to demonstrate any association between *UCP* polymorphisms and obesity; however, in the meta-analysis we detected a significant association of *UCP2* −866G/A, Ins/Del, Ala55Val and *UCP3* −55C/T polymorphisms with obesity.

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Diabetes complications

P403

Does proton pump inhibitor use decrease microvascular complicaton rate in type 2 diabetic patients? A retrospective analysis

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Proton pump inhibitor (PPI) drugs which are used safely to treat peptic ulcus disease since 2 decades, moderately increases gastrin hormone by decreasing gastric acid secretion. Preclinical studies show that gastrin itself, or drugs that increase gastrin levels such as PPIs, increase islet cell mass and improve glycaemic control. To the best of our knowledge one prospective and some retrospective studies claim that PPI medication in diabetic patients leads to an average decrease of % 0.5–0.8 in HbA1c. According to UKPDS a 1% decrease in HbA1c prevent microvascular complication by 37%. Therefore, we aimed to investigate the effect of PPI drugs on microvascular complications in a sample of patients applied to a university outpatient clinic. The PPI treated group enrolled 37 patients, while the non-PPI group consisted of 51 patients. Selected PPI using patients were treated at least for 5 years in intervals with various PPIs. The mean PPI use duration was 11.3 ± 4.5 (6–24) months. The non-PPI group did not use any PPI longer than 1 month intervals in the last 5 years. All statistical comparisons were made by adjusting both groups according to age, diabetes duration, and mean HbA1c. Mean ages in the PPI and non-PPI group were 68.1 ± 9.9 and 67.2 ± 8.5 respectively ($P = 0.57$). Mean diabetes duration in the PPI and non-PPI group were 11.1 ± 8.5 and 9.2 ± 4.1 respectively ($P = 0.13$). Mean HbA1c percentages in the PPI and non-PPI group were 6.9 ± 1.1 and 6.9 ± 1.2 respectively ($P = 0.79$). Mean follow-up duration of the whole study population was 48.6 ± 36.9 (6–139) months with a median of 4 (2–7) HbA1c measurements *per se*. Microvascular complication rates are shown in Table 1. We conclude that although neuropathy rate was insignificantly lower on PPI, the use of PPIs does not affect microvascular complication rates in diabetic populations.

Table 1

	PPI status		
	PPI (%)	Non-PPI (%)	*P* (95% CI)
Nephropathy	13.7	5.4	0.293
Retinopathy	19.6	15	0.782
Neuropathy	13.2	23.7	0.265

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P404

The relation of left ventricular hypertrophy and markers of inflammation in type 2 diabetic patients

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Introduction
The association between diabetes and adverse cardiovascular outcome may be partially explained by the strong independent association of type 2 diabetes with cardiovascular target organ damage, such as left ventricular hypertrophy (LVH), a well-known predictor of cardiovascular events independent of coronary artery disease. The aim of the present study is to evaluate the relation of LVH to fibrinogen and C-reactive protein (CRP) as markers of inflammation and susceptibility to atherothrombosis.
Methods and subjects
We selected 50 adults with type two diabetes. 32 were women and 18 were men, mean age 45 ± 14. Hypertension was defined by systolic blood pressure (sBP) 140 mmHg and/or diastolic blood pressure (dBP) 90 mmHg. Diabetes was defined by fasting plasma glucose levels 126 mg/dl or by specific treatment. BMI was calculated by the standard formula.
Echocardiography methods
The prevalence of left ventricular abnormalities has been determined by bidimensional echocardiography. The left ventricular mass index (LVMI) has been evaluated according to the method of Devereux and Reichek.
Participant's laboratory data were examined in the morning after an overnight fast 12 h. The levels of CRP and fibrinogen have been measured.
Results
From 50 participants, 22 (44%) presented LVH, which was associated with higher BMI and CRP, fibrinogen levels, left ventricular hypertrophy, markers of inflammation. We found relationships between fibrinogen and concentric LVH ($P < 0.001$) and also between CRP with concentric hypertrophy ($P < 0.005$).
Conclusions
22 patients presented concentric LVH, ten patients eccentric LVH, and 18 patients normal LV mass. Concentric LVH was associated with elevated markers of systemic inflammation and susceptibility to atherothrombosis (CRP and fibrinogen levels) independently of clinically overt cardiovascular disease and traditional cardiovascular risk factors. No correlation was found between CRP and fibrinogen and eccentric LVH.

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P405

Incidence and cost of complications among men and women with type 2 diabetes

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Aims/Introduction
To evaluate the impact of diabetes mellitus on the incidence of related micro- and macrovascular outcomes as well as cost analysis in people with type 2 diabetes mellitus.
Materials and methods
In a cohort study, registered patients with type 2 diabetes mellitus were followed for 10 years at a tertiary care center. The type of medications and clinical data were extracted from patients' archives. Incidence of mortality, micro- and macrovascular complications recorded in patients' documents was analyzed. For economic evaluation, para clinic and inpatient costs were calculated.
Results
From 1562, patients with type two diabetes mellitus, a total of 1,000 patients with mean duration disease of 11.2 years, were followed. Mean cumulative incidence of diabetes-related events over 10 years were 10.9 ± 3.5, 8.0 ± 3.1, 4.6 ± 1.7, 9.1 ± 3.6 and 2.3 ± 0.9% for neuropathy and diabetic foot, nephropathy, ophthalmic complications, cardiovascular disease and death, relatively. Average para clinic and inpatient costs per patient were 393.6 ± 47.8 and 1520.7 ± 104.5 USD correspondingly.
Conclusions
Our findings demonstrate high incidence and health care expenditure of type 2 diabetes-related complications among our patients. However, as the number of people with diabetes rises, so early detection and development of therapeutic strategies to decrease the incidence of type 2 diabetes mellitus complications are necessary.

Keywords
Cost of illness, incidence, type 2 diabetes
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P406

Is the ankle-brachial index directly associated with current glycemic control in diabetic patients? Preliminary results of our study

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Introduction
Association between ankle-brachial index (ABI) and coronary, cerebral, and peripheral vessels involvement has been shown in different studies. The normal range of ABI is between 0.9 and 1.4. Values below 0.9 show peripheral vessel disease. An ABI more than 1.4 is characteristic for vascular rigidity. We aimed to investigate the ABI value in our type 2 diabetic patients and association of ABI with glycemic control.
Materials and methods
This cross-sectional study was performed on 136 type 2 diabetic patients. Ankle systolic blood pressure was measured on posterior tibialis arteries by using IABP-hand Doppler. ABI was calculated as as the highest ankle systolic pressure divided by highest brachial systolic pressure in each patient.
Results
95 females and 41 males were examined, mean age 54.4 ± 4 years. The mean duration of diabetes was 118.6 ± 89.2 months. The mean A1c level was 8.03 ± 1.7%. According to ABI values, there was only one patient whose ABI below 0.9. Peripheral arterial pulses was intact for this patient. 65.6% of our patients were within normal ABI value (0.9–1.4). 33.5% of our diabetic patients had ABI value of >1.4. When diabetic patients were categorized into three different groups based on A1c, <7, 7–9 and >7; ABI value did not show any significant difference between groups ($P = 0.472$). When analysis was performed based on vascular complication status, ABI value was not statistically different between two groups which were group with and without vascular complications ($P = 0.901$). There was no correlation of ABI value with A1c, duration of diabetes.
Conclusion
Approximately 34% of our patients had high ABI. In our study, ABI was not found as correlated to the current degree of glycemic control which is indicated by A1c. There is a need for further investigation of potential relationships between abnormal ABI and prevalence of coronary heart disease among type 2 diabetics.

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P407

Abstract unavailable.

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P408

Angiogenic factors and circulating endothelial progenitor cells in patients with type 2 diabetes mellitus

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Introduction
Abnormal angiogenesis may contribute to impaired wound healing and the consequence of them is non-healing diabetic ulcers development. Therefore, the aim of the study was to evaluate the number of circulating EPCs, plasma levels of VEGF-A, sVEGF-R2 and FGF-2 in diabetic patients.
Materials and methods
Totally, 75 subjects were enrolled: 45 patients with type 2 diabetes (mean age 67.1 years) and 30 healthy volunteers (mean age 63.3 years). Patients were divided into two groups: 23 with DF (diabetic foot) and 22 without DF. VEGF-A, sVEGF-R2 and FGF-2 plasma concentrations were measured by ELISA. The number of EPCs was determined by flow cytometry.
Results
The results were presented in the table below.

Table 1

Par-ameter	Patients with DF Me(Q1;Q3) I $n=23$	Patients without DF Me(Q1;Q3) II $n=22$	The control group Me(Q1;Q3) III $n=30$	P value
VEGF-A (pg/ml)	36.0 (13.74;73.95)	79.16 (29.56;131.55)	15.06 (7.98;27.84)	I vs II $P=0.04$ I vs III $P=0.01$ II vs III $P=0.0002$
sVEGF-R2 (pg/ml)	8930.5 (8360.0; 10 356.0)	10 099 (8765.2; 10 841.5)	10 738.75 (9670.5; 11 766.0)	I vs II $P=0.2$ I vs III $P=0.007$ II vs III $P=0.07$
EPCs/μl	0.41 (0.2;1.22)	0.31 (0.1;1.53)	0.41 (0.2;0.92)	I vs II $P=0.0581$ I vs III $P=0.7$ II vs III $P=0.6$
FGF-2 (pg/ml)	6.39 (5.54;8.42)	4.97 (4.45;6.02)	4.92 (4.6;5.44)	I vs II $P=0.0002$ I vs III $P=0.000003$ II vs III $P=0.8$

A significant negative correlation between EPCs and diabetes duration was observed ($P=0.03$, $r=-0.43$). Conclusions: The study demonstrated that diabetic patients with DF showed decreased VEGF-A and increased FGF-2 levels compared to the patients without DF. It might be associated with impaired angiogenic response.

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P409

Associated study of polymorphic variants in the gene for superoxide dysmutase (Mn SOD) and different types of diabetes mellitus

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Superoxid dysmutase (SOD) is a key antioxidant enzyme engaged in detoxication of superoxide radicals. Ala/Val substitution in Mn SOD leads to a change in the effectiveness of the action of the enzyme. This polymorphism we analyzed among several groups patients with diabetes and we compared with control group of healthy volunteers. It is proved an association connection of tracked marker in some of the groups of patients with diabetes compared to the rest population sample. Such a study is made for the first time in Bulgaria, and indicates that, polymorphic allele is meeting in- often in some of the groups of diabeticions, as the difference in frequencies relative to the control sample is statistically reliable.
Methodology
In this study a case–control we had examined patients with different types of diabetes mellitus and a control group of healthy persons.
The polymorphism Ala(−9)Val in Mn–SOD gene represents a substitution at position −9 leading to schematic amino acid substitution of alanine with valine.
The genotyping of selected groups of patients and the control sample included amplification of area of Mn–SOD gene with primers containing nucleotide discrepancy creating place recognized of restrictase BshTI. So the amplificated product with length 91nucleitides, visualized after electrophoresis separation as two fragments of length 17 and 74 nucleotide pairs in the presence of polymorphic allele.
Results
In comparing the allele frequencies and genotyping frequencies in the group of patients with diabetes mellitus type 1 and type 2 and the control sample of Mn-SOD polymorphisms was not established statistically significant difference.
Patients with diabetes mellitus type 2
The allele containing restrictation place Val (+) is meeting emphasized in- often in the group with DM type 2, with an increase of the sampled group may be expected to reach statistical reliable difference.
Statistical analysis shows that the genotype containing allele (+Val) in homo- or heterozygote condition compared with allele (−Ala) shows statistical significant difference in this group. It can be interpreted that polymorphic genotype is associated with susceptibility to this type diabetes.
Patients with DM type 1
Established statistically significant difference when comparing the allele frequencies in the group of patients with diabetes mellitus type 1, and a control sample of Mn-SOD polymorphisms. And in this group polymorphic allele occurs more often in the group of patients, the difference in frequencies relative to the control sample is statistically reliable.
In comparing the genotype frequencies shows that, the polymorphic genotype excel in – highly in homozygote condition and is meeting statistical in – often in patients with diabetes type 1.
Discussion
No effective action of Mn–SOD is following of leaving the mitochondria without to exercise full protection against superoxid radicals. This leads to increase the protein oxygenation as mitochondrial DNA mutations and damage, a frequent event in the pathogenesis of diabetic polyneuropathy.
The functional role and the possible association with diabetic pathology determined SOD genes as an interesting subject for associated studies.

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P410

Depression risk factors in type 1 diabetes mellitus

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Purpose
To evaluate the possible risk factors for depression development in type 1 diabetes mellitus (DM 1).
Methods
163 patients with DM 1. Depression was determined by the hospital anxiety and depression scale (HADS). Common factors of risk depression development were assessed by questionnaire survey according to a specially designed questionnaire. The levels of HbA1c and homocysteine (HC) serum were determined.
Results
Depression was diagnosed in 28.2% of the study, among them 18.4% women and 9.8% men ($\chi^2=3.57$; $P<0.05$). Median of the depression level according to the HADS in the age group under 40 years was 3 (2, 7) points against 6 (3, 8) points in patients older than 40 years ($U=2698.0$; $P=0.04$). There has been established a direct correlation between the level of depression according to the HADS and age ($r=0.17$; $P<0.05$); between the level of depression according to the HADS and HbA1c level ($r=0.20$; $P<0.05$). Median of HC plasma level in patients with depression was 13.29 (15.90 8.80) mmol/l against 9.80 (7.94 11.50) mg/dl in patients without depression ($U=15.12$; $P=0.02$). The frequency of diabetic retinopathy (DR) in patients with depression was 95.6% against 57.2% in patients without depression ($\chi^2=4.12$; $P=0.04$). The frequency of diabetic nephropathy (DN) in patients with depression was 52.1% against 22.2% in patients without depression ($\chi^2=6.78$; $P=0.009$).
Conclusion
The risk of depression development is associated with female sex (OR=3.60; $P<0.001$; 95% CI 1.76–7.39), age over 40 years (OR=1.06; $P<0.05$; 95% CI 0.99–1.13), the presence of disability because of DM (OR=2.41; $P=0.01$; 95% CI 1.16–4.19), the presence of DR and/or NAM, the level of serum HC> 15.39 mmol/l (OR=6.82; $P=0.001$; 95% CI 2.19–21.20), the level of HbA1c≥7.5%, (OR=0.89; $P=0.03$; 95% CI 0.30–1.48).

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P411

Disabilities of the arm, shoulder and hand 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 and symptoms. The DASH consists mainly of a 30-item disability/symptom scale. In this study, we aimed to evaluate DASH questionnaire in 1000 type 2 diabetes mellitus (DM) patients.
Material and methods
179 patients (mean age 51.73 ± 9.06 years, 117 women and 62 men) who had type II DM 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. 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 7.32 ± 5.97 years. Dupuytren's contracture was present in 6.1%, cheiroarthropathy in 11.2%, tinnel sign in 21.2% and tendinitis in 5%. Retinopathy was present in 17.9%, nephropathy in 17.3%. DASH score was 70.35 ± 34.50. Mean BMI was 31.88 ± 5.90. Mean TBF was 28.95 ± 11.91 kg. Mean %BF was 33.93 ± 10.10. There was positive correlation between DASH score and cheiroarthropathy, tinnel sign, tendinitis and Dupuytren's contracture ($P=0.009$ $r=196$; $P=0.002$, $r=246$; $P=0.001$, $r=299$; $P=0.028$, $r=164$ respectively). There was positive correlation between DASH score and BMI and TBF and %BF ($P=0,000$, $r=336$; $P=0.000$, $r=290$; $P=0.000$, $r=304$ respectively). There was positive correlation between DASH score and diabetic nephropathy ($P=0.028$, $r=164$) No correlation was found between DASH score and diabetic retinopathy.
Conclusions
DASH questionnaire is useful instrument for measuring functional disability in upper extremity complaints of diabetes mellitus patients. It should also be taken into consideration in order to increase the quality of life in DM patients.

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P412

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 (DM) patients.
Material and methods
179 patients (mean age 51.73 ± 9.06 years, 117 women and 62 men) who had type II DM 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 7.32 ± 5.97 years. Dupuytren's contracture was present in 6.1%, cheiroarthropathy in 11,2%, tinnel sign in 21.2% and tendinitis in 5%. Retinopathy was present in 17.9%, nephropathy in 17.3%. BDI score was 14.894 ± 10.73 and BAI score was 17.80 ± 14.87. There was positive correlation between BDI score and diabetic nephropathy ($P=0.000$, $r=314$). Also there was positive correlation between BDI score and tinnel sign ($P=0.000$, $r=303$). Positive correlation between BAI score and diabetic nephropathy was detected ($P=0.003$, $r=217$). There was positive correlation between BAI score and cheiroarthropathy, tendinitis and tinnel sign ($P=0.023$, $r=170$; $P=0.039$, $r=155$; $P=0.000$, $r=315$ respectively). The suggested BDI cutoff of ≥ 17 had 81% sensitivity and 79% specificity and classified as clinically depressed. In our study BDI score ≥ 17 was 34.6%. BAI score ≥ 17 was classifed as moderate and serious anxious. In our study BAI score ≥ 17 was 43%.
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
In this study, our aim was to investigate the prevalence of the most frequently occurring hand complications in 1000 type 2 diabetes mellitus patients.
Material and methods
179 patients (mean age 51.73 ± 9.06 years, 117 women and 62 men) who had type II DM 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 7.32 ± 5.97 years. Dupuytren's contracture was present in 6.1%, cheiroarthropathy in 11.2%, tinnel sign in 21.2% and tendinitis in 5%. Retinopathy was present in 17.9%, nephropathy in 17.3%. Mean HbA1c was 8.70 ± 2.06. Mean fasting glucose was 183.22 ± 74.16 mg/dl. The mean urinary albumin excretion was 61.33 ± 19.47 mg/day. Mean creatinine clearence was 89.91 ± 32.20 ml/min. The relationship between these complications and patients' age, sex, duration of diabetes and glycaemic control was also analysed. There was positive correlation between age and cheiroarthropathy and dupuytren's contracture ($P=0.006$, $r=203$ and $P=0.000$, $r=296$ respectively). There was positive correlation between diabetic duration and diabetic retinopathy ($P=0.000$, $r=298$). There was positive correlation between diabetic duration and cheiroarthropathy ($P=0.016$, $r=180$). There was positive correlation between diabetic nephropathy and cheiroarthropathy, tinnel sign and tendinitis ($P=0.004$, $r=213$; $P=0.009$, $r=196$; $P=0.067$, $r=165$ respectively).
Conclusions
Some musculoskeletal disorders are more prevalent in type 2 diabetes mellitus 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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P414

The results of evaluation of dynamics of levels of glycemia in diabetes mellitus type 1

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The aim of the work was to assess the dynamics of rates of carbohydrate metabolism in DM1 in young persons.
Materials and methods
The study of daily dynamics of glucose was conducted by Continuous Glucose Monitoring System. For the analysis of continuous glycaemic curve there was conducted the computation of risk index (RI) of hypoglycemia and hyperglycemia during the study period.
There were examined 162 patients with DM1. First group with adequate control DM1, HbA1c $\leq 7.5\%$ ($n=38$), which is 23% and second group with inadequate

control, HbA1c > 7.5% ($n = 124$), which is 77% of the total number of examined persons. Groups are comparable by average age (28.59 ± 7.10 years), duration of DM1 (10.46 ± 7.28 years), BMI (24.12 ± 3.62 kg/m^2).
Results
Adequate control of DM1 was only in 23% of examined patients, in 77% there has been noticed decompensation of DM1 ($P < 0.05$). In the group with HbA1c > 7.5% there has been noticed decompensation of DM1 due post-hypoglycemic hyperglycemia (RI of hypoglycemia 5.00 (1.60; 9.20), RI of hyperglycemia 16.24 (10.45; 20.60)). In both groups RI of hypoglycemia exceeded 4.5 (group with HbA1c ≤ 7.5% 5.60 (3.00; 10.50), group with HbA1c > 7.5% 5.00 (1.60; 9.20)), which indicate a high risk of development of hypoglycemic reactions. In the group with adequate control hypoglycemic episodes have been registered in 82% of the patients and only 18% didn't have them ($P < 0.001$).
Conclusion
In 77% of the examined patients with DM1 there have not been achieved target values of compensation, which is approved by the increased value of RI hypo-and hyperglycemia. Decompensation of DM1 is caused by posthypoglycemic hyperglycemia.

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P415

Analysis of diabetic retinopathy risk factors in type 2 diabetes patients

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Introduction
Diabetic retinopathy screening is the most accessible method of visualization of the affected small blood vessels in diabetic patients. Diabetic retinopathy is associated with age of patients, duration of diabetes, male sex, poor blood glucose control, central obesity, arterial hypertension, increased proteinuria, chronic inflammation and lipid disorders. Our study aims to compare type 2 diabetes patients with and without developed diabetic retinopathy regarding traditional culprits for diabetic retinopathy development and also to analyze differences in therapy modules between two mentioned groups.
Methods/design
Cross-sectional study included 140 type 2 diabetes patients. Patient's general information were noted, anthropometrical measurements (BMI, waist circumference (WC) and arterial tension) were conducted, blood was sampled for glucose, lipid and lipoprotein metabolism parameters (HbA1c, total, LDL and HDL cholesterol and triglycerides) and fibrinogen, and 24 h urine portion was sampled for proteinuria measurement. Classical fundoscopy was performed in all patients. In statistical analyzes we used mean values, proportions, *t*-test, test of proportions and multivariate analysis.
Results
In group with developed diabetic retinopathy there were 74 patients and more often they were males ($P = 0.0218$). They were older ($P = 0.0009$) and had longer duration of diabetes ($P = 0.0002$). WC was significantly higher in this group ($P = 0.0018$), and they had higher levels of proteinuria ($P = 0.0018$). As far for therapy modules, these patients were rarely on oral therapy only ($P < 0.0001$), they were less frequently on sulphonylureas ($P = 0.0030$) and more often had insulin in therapy ($P < 0.0001$). Multivariate analysis stands out male sex ($P = 0.0071$), age ($P = 0.0029$), WC ($P = 0.0051$), proteinuria (0.0077) and solely oral therapy ($P < 0.0001$).
Conclusion
Our type 2 diabetes patients with diabetic retinopathy are more often males. They are older, more centrally obese, have higher proteinuria and more frequently are on insulin therapy than patients without this complication which is mostly in accordance with other literature on the same topic.

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P416

Treatment of ulcer-necrotic manifestations of diabetic foot using ultrasonic cavitation

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Around 90–95% of all patients with DM have type 2, among whom 90% could likely suffer from ulcerative-necrotic manifestations of diabetic foot (DF). The latters may develop neuropathic form of DF in 80% of cases. To examine the effectiveness of treatment of ulcers in patients with the neurotic form of DF using ultrasonic cavitation.
57 patients with DM type 2 were treated who had the neurotic form of DF with 1–3 degrees of ulcers on the feet according to the Wagner classification. Compensation of diabetes was achieved by administering insulin regardless of previous hypoglycaemic therapy. Pending the results of bacteriological examination of the wound content the following groups of antibiotics were empirically prescribed: fluoroquinolones, penicillins, lincosamides, cephalosporins (first-generation). After receiving the results of the sensitivity of the wound microorganisms appropriate antibiotics were appointed according to this sensitivity. All patients had wound clearing according to treatment of wounds systemized by Qoustic model AR1000. The Qoustic is equipped with a domed device that allows dual supply of activated solution. The ultrasound energy was focused on the wound together with the application of sterile saline solution which resulted in tiny vibrating gas bubbles that separated dead and damaged cells from healthy tissue (cavitation). Ultrasonic vibration itself can also separate, destroy and remove non-viable tissue. This procedure was repeated once a day 3–6 times for each patient until achieving complete cleaning of the wounds. In order to compare, patients of the control group received the same medication with application of only necrotomy on the wound. Patients in both groups were superimposed by bandages with 10% povidone-iodine solution twice a day.
Epithelialization of ulcers in patients treated with the use of ultrasonic cavitation began after 2–3 days of the cavitation procedure with complete cleaning in 5–6 days, while the control group needed 4–6 and 9–12 days respectively.
The use of ultrasonic cavitation in treatment of ulcerative-necrotic lesions in patients with DF accelerates wound cleaning and healing and reduces the time of patients' hospitalization, which leads to significant increase in effectiveness of the treatment both financially and socially.

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P417

Genetic dependence of urinary enzyme, neutral α-glucosidase, in diabetic nephropathy in uzbek children and adolescents with type 1 diabetes mellitus

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The work was initiated to assess clinical-diagnostic value of urinary α-glucosidase activity in predicting chronic renal insufficiency in type 1 diabetes mellitus in Uzbek children and adolescents. We examined 152 children and adolescents of the Uzbek population, 122 children and adolescents with type 1 diabetes mellitus (51 male and 71 female). By proteinuria the patients were divided into three groups: with normoalbuminuria (NAU) ($n = 52$), with microalbuminuria (MAU) ($n = 50$) and marked proteinuria (MPU) ($n = 20$). 30 children and adolescents of matched age and sex were included into the control group. The urinary neutral α-glucosidase activity was measured by rate of glucose formation from maltose. In Uzbek children and adolescents with type 1 diabetes mellitus high incidence of D-allele was observed as diabetic nephropathy progressed. II Genotype was registered in 41.5% of cases on the MAU stage, but no cases were observed on MOU stage to be the evidence for high protection of the ACE gene genotype in chronic renal insufficiency progression and consistent with data of studies conducted in other ethnic populations. For the first time the study on interconnection between activity of urinary neutral α-glucosidase activity and ACE gene genotype was performed. It was established that urinary neutral α-glucosidase activity depended not only on diabetic nephropathy (DN) severity, but on all DN stages in persons with ID and DD genotype it was confidently higher than in those with II genotype. That is the activity of the enzyme was turned out genetically determined by ACE gene. The findings broaden diagnostic opportunities in assessment of urinary neutral α-glucosidase activity not only in early diagnosing of pre-clinical DN in children and adolescents with type 1 diabetes mellitus, but also in predicting progression of terminal DN stages in patients with high susceptibility to chronic renal

insufficiency. Registration of increase in the urinary neutral α-glucosidase in children and adolescents with type 1 diabetes mellitus on the pre-MAU stage as a marker of early pre-clinical DN stage will allow solving problem of identification of a group with confidently high DN predicting and progression risk as well as preventive therapy of the complication in question.

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P418

Activity of neutral α-glucosidase in the urine of children and adolescents with type 1 diabetes mellitus and diabetic nephropathy

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Aim
To identify clinical significance of enzymuria in early diagnosis of DN in children and adolescents with type I diabetes mellitus.
Materials and methods
We examined 112 patients (47 males/55 females) with type I diabetes mellitus. By the DN severity the patients were divided into following groups: with normoalbuminuria (NAU) ($n=47$), with microalbuminuria (MAU) ($n=44$) and with marked proteinuria (MP) ($n=19$). Ten healthy subjects of the same age were included into the control group. Activity of neutral urinary α-glucosidase (α-GL) was measured by intensity of glucose formation from maltose after its incubation in potassium phosphate buffer containing 0.2 mMol/l of maltose at 37 °C.
Results and discussion
The study showed confident increase in the urinary protein level with DN progression. As compared with the NAU persons there was a six-time increase of the urinary protein in patients with MAU (13.6 ± 0.7 vs 77 ± 9.5), in patients with MP the protein increase being 32 times higher as compared with those with NAU (13.6 ± 0.7 vs 416.8 ± 50.78). In patients with NAU prior to MAU appearance activity of neutral α-GL confidently increases by 36 times (0.01 ± 0.032 vs 0.52 ± 0.041), in patients with MAU there was a 1.5-time increase as compared with NAU persons (0.36 ± 0.032 vs 0.52 ± 0.041), in the group with MP the parameter increasing by 1.2 times as compared with the patients having MAU (0.52 ± 0.041 vs 0.61 ± 0.04).
Conclusions
In children and adolescents with type I diabetes mellitus increase in the activity of the urinary neutral α-glucosidase was established associating with disturbance of both renal tubular and glomerular apparatuses to correlate with the proteinuria and DN severity. As DN severity enhances the activity of the urine neutral α-GL is shown to increase. An early marker in DN diagnosis activity of the urinary neutral α-GL is found diagnostically significant at the early stages of diabetes mellitus progression

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P419

Prevalence and risk factors of prolonged QTc interval in type 2 diabetic patients; impact of the type of treatment and quality of glycemic control

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Introduction
The aim of this study was to assess the prevalence and predictors of prolonged QTc interval in patients with type 2 diabetes (T2D).
Methods
This study included 501 consecutive T2D patients (277 males, age 60.4 ± 8.1 years) treated in National Educational Centre for Diabetes, 'Merkur', Vrnjacka Banja, from September 2011 to July 2012. We analysed baseline clinical and laboratory data including: age, gender, duration of diabetes, BMI, presence of coronary artery disease (CAD), presence of polyneuropathy, type of treatment, renal function, and the presence of traditional risk factors for CAD. In all patients 6–8 blood samples were taken within 24 h and following parametres of glycoregulation were analysed: fasting blood glucose (FBG), mean blood glucose (MBG), and mean amplitude of glucose excursion (MAGE), as well as HbA1c. In baseline ECG corrected QT interval (QTc) was measured, considering QTc > 440 ms as prolonged, and QTc > 500 ms as significantly prolonged.
Results
Prolonged QTc (> 440 ms) was present in 44% of our patients, however, prolongation of QTc > 500 ms was observed in only 2% of patients. QTc duration > 440 ms was associated in univariable analysis with age, female gender, treatment with sulfonylurea, and different parametres of glycemic control (HbA1c, FBG, MBG, and MAGE) as well as with the history of CAD and presence of diabetic polyneuropathy. However, MBG ($B=2.192$, $P<0.001$), female gender ($B=8.844$, $P<0.001$), history of CAD ($B=8.636$, $P=0.001$), and treatment with sulfonylurea ($B=5.198$, $P=0.027$) remained independently associated with QTc > 440 ms in multivariable analysis. On the other hand, QTc > 500 ms was independently related only to the history of CAD and MBG (OR = 12.145, 95% CI 1.818–81.146 and OR = 1.457, 95% CI 1.154–1.840 respectively, $P<0.001$ for both).
Conclusions
QTc > 440 ms was highly prevalent (44%) in our T2D patients, with only minority of them (2%) exhibiting QTc prolongation over 500 ms that was independently related to the mean blood glucose and the history of CAD.

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P420

Patients with type 1 diabetes and thyroid autoimmunity have low prevalence of microangiopathic complications

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Introduction
Type 1 diabetes (T1DM) is often associated with autoimmune thyroid disease (AITD). Common susceptibility genes increase risk for development of both AITD and T1DM. The influence of this comorbidity on the risk of diabetic microangiopathy is unknown.
Methods/design
We included 100 consecutive patients with T1DM (55 men, and 45 women) aged 29 (mean, SD = 6) with diabetes duration 13 (6) years, 35 had diagnosed at least one microangiopathic complication (retinopathy or nephropathy or neuropathy). Exclusion criteria were: history of thyroid disease, current treatment of L-thyroxin or anti-thyroid drugs.
Anti-thyroid peroxidase (aTPO) and anti-thyroglobulin (aTg) antibodies, anti-TSH receptor antibodies (TRAb) were determined using a luminescence method. Assays for TSH and free thyroid hormones (triiodothyronine, fT_3, and thyroxin, fT_4), as well as thyroid ultrasonography (USG) were also performed. In statistical analysis Fisher exact test and multivariate logistic regression were used.
Results
The prevalence of thyroid autoimmunity (positivity for aTPO or aTg) in the study group was 31% (19 women, and 12 men). 8% of patients were only positive for ATPO and 5% only for ATg, no patients were positive for TRAb. Subclinical hypothyroidism was diagnosed in 9%, and overt hypothyroidism in 2% of patients. Among patients with anti-thyroid autoimmunity prevalence of microangiopathy was lower than in patients without positive titre of aTPO and aTg: 3 of 31 (10%) vs 32 of 69 (46%), $P=0.0003$. In multivariate logistic regression model presence of anti-thyroid antibodies was associated with lower odds of microangiopathy independently of sex, age, BMI, cigarette smoking, systolic blood pressure, HbA1c value, serum TSH and LDL-cholesterol concentrations (OR 18.3, 95% CI: 3.7–89.6, $P=0.0003$).
Conclusion
Thyroid autoimmunity was associated with lower rate of microangiopathic complications in patients with T1DM. Prospective studies are needed to determine the causality of this finding.

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P421

Relationship between diabetes mellitus and hemostasis: a prothrombotic condition

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Background
Diabetes is very common disorder. Many studies have shown that patients with diabetes mellitus have incresing trombotic complications both arterial and venous trombosis. Bad control diabetes increases risk of trombosis. Recent reports have shown that shortened APTTs and increased fibrinogen indicate procoagulan situations. In this study, we aimed to evaluate whether chronic hyperglisemia or bad control diabetes causes trombosis which is reflected by shortened APTTs and increased fibrinogen.
Materials and methods
Our study included 349 patients with type 2 diabetes mellitus. They all underwent blood sampling APTT, PT, fibrinogen, fasting plasma glucose (FPG), postprandial plasma glucose (PPG), complete blood count(CBC), serum lipids and HBA1C measurements. Among 349 patients whose APTT $<$ 22 sec and PT $<$ 10.5 sec were determined. Patients were divided into two groups based on HBA1C levels as follows: regulated diabetic group (HBA1C $\leq$ 7.0%) and disregulated diabetic group (HBA1C $>$ 7.0%).
Results
But there was no significant difference in terms of APTT $<$ 22 sec, PT $<$ 10.5 sec and fibrinogen levels between two groups.
Conclucion
APTT, PT and fibrinogen measurements are relatively inexpensive and are available. But they are not enough alone for evaluating hypercoaguable states in diabetes patients.

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P422

Androgendeficiency in men with type 2 diabetes mellitus

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Introduction
The issue of the impact of disturbances of functional status of gonads in men on the development of type 2 diabetes mellitus (T2DM) has been studied for a long time. However, the results obtained appear to be ambiguous. A number of studies conclude that blood levels of testosterone (T) in men with DM are within the normal range of fluctuations and do not play a pathogenetic role. At the same time, recent epidemiological studies demonstrate a high prevalence of low T levels in the blood of men with T2DM.
Material and methods
Androgen's levels and functional status of hypophyseal–gonadal system has been assessed in147 men aged from 35 to 65 years with T2DM and 82 practically healthy men. Using an immunoenzymic method, blood concentrations of the following hormones were tested: FSH, LH, total testosterone (tT), free testosterone (fT), bioavailable testosterone (bT), dihydrotestosterone (DHT), and sex-steroid-binding globulin (SSBG).
Results
The average blood level of tT in study patients was significantly decreased. Marked fluctuations of hormone concentrations from 2.3 to 29.9 nmol/l were noted. An analysis of individual indices in certain patients showed a decreased hormone level ($\leq$ 11.7 nmol/l) in 43.5% men with T2DM. It has been established that in 19.0% patients with T2DM tT level was below 8.0 nmol/l, and in 34.0% men was within the range 8.0–12.0 nmol/l. Blood concentration of fT was below the lower limit of normal hormone range in 59.1% of study subjects. The average level of bT was significantly decreased, as well, in 69.6% of males with T2DM (7.7 ± 0.7 nmol/l in T2DM patients vs 13.4 ± 1.1 nmol/l in controles, $P < 0.001$). SSBG blood levels were decreased or within the lower limit of normal range in 2/3 T2DM male patients group: 36.3 ± 1.3 vs 43.1 ± 2.3 nmol/l in control group ($P < 0.01$). No differences were observed in LH and FSH levels among both groups. Study of DHT blood concentrations in patients with T2DM suggested decreased levels irrespective of severity, compensation of metabolic disturbances, diabetes course and duration.
Conclusion
Men with type 2 diabetes mellitus are at risk group for development androgendeficasy. For the estimation of the state of the androgen supplementation its necessary to determine total and bioavailable T levels, as well.

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Characteristic features of the course of chronic venous insufficiency of the lower limbs in patients with impaired peripheral innervation of diabetes mellitus type 2

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Purpose
To assess the influence of diabetic polyneuropathy (DPN) on the course of chronic venous insufficiency (CVI) of the lower limbs in patients with combined pathology.
Methods
40 patients with CVI of the lower limbs in combination with diabetes mellitus (DM) type 2 were examined. DPN was diagnosed in 34 patients - group 1, 6 patients had no DPN - group 2. The diagnosis of CVI was established according to the international classification of CEAP. The intensity of subjective symptoms of CVI was assessed using Venous Clinical Severity Score (VCSS). Neurological examination included the use of the Neuropathy Disability score (NDS) and electroneuromyography (EMG).
Results
The patients in group 2 varicose changes had more often: 50% versus 11.7% in group 1 ($P = 0.02$), in group 2 trophic changes prevailed: 53% versus 0% ($P = 0.01$). A significant difference in VCSS was revealed: in group 1 $-$ 9.6 3.2, in group 2 $-$ 6.3 1.7 points ($P = 0.01$). In patients with DPN a positive correlation between the NDS and severity of CVI ($r = 0.43$; $P = 0.01$) and between the NDS and VCSS ($r = 0.5$; $P = 0.002$) was determined. Analyzing individual subjective manifestations of CVI using VCSS, in group 1 there was a positive correlation between the NDS and hyperpigmentation ($r = 0.45$; $P = 0.007$), NDS and induration ($r = 0.44$; $P = 0.008$). According to the results of EMG in patients with DPN and trophic changes of the lower limbs M-response amplitude on n. Tibialis 3.4 [2.2;6.1] mV and n. Peroneus 1.4 [1.0;3.5] mV , as well as speed of propagation of excitation (SPE) on n. Peroneus 42 [39; 44] m/s and n. Suralis 27 [21;39] m/s were significantly lower compared with patients without trophic changes, which M-response amplitude on n. Tibialis 6.4 [5.2;7.1] mV ($P = 0.01$) and n. Peroneus 3.7 [2.5; 4.6] mV ($P = 0.002$) for the speed of propagation of excitation n. Peroneus 45 [42;48] m/s ($P = 0.02$) and n. Suralis 39 [36;42] m/s ($p = 0.009$)
Conclusion
DPN aggravates the CVI in patients with DM type 2. The defeat of the sensory and motor fibers according to EMG is associated with more serious trophic disorders caused by chronic venous insufficiency.

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Abstract unavailable.

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P425

Benfotiamine efficiency in the stabilization of diabetic peripheral polyneuropathy

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One of the most frequent complications of diabetes is diabetic sensorimotor peripheral polyneuropathy (DSPN). B vitamins successfully used for the treatment DSPN. However, prolonged use of vitamins B6 and B12 in effective doses limited by the comorbidities and possibility of the neurotoxic reactions development, as for vitamin B1, its low bioavailability of water-soluble forms. This determines whether the use of fat-soluble form of benfotiamine with maximum bioavailability.

Goal

To evaluate the efficacy of using benfotiamine monotherapy (Milgamma mono) in the stabilization of DSPN after achieving therapeutic result.

Materials and methods

The study included 34 patients with DSPN. All patients obtained Milgamma injections N5 and then Milgamma dragees (three tablets per day) for a month. After washout period, the patients were divided into two groups: Group 1 - stopped treatment after achieving a therapeutic effect ($n=21$), Group 2 - continue treatment with Milgamma mono 300 per day for 2 months ($n=13$). Rating pain in legs conducted by visual analog scale (VAS), and the severity of DSPN rated on standard scales NSS, TSS, NDS and electromyography (EMG).

Results and discussion

The significant positive trend in all performance indicators were registered after washout period in all patients included in the trial. After randomization into groups and by the end of treatment in Group 2 there was a significant positive trend compared to Group 1 and the initial result. VAS day decreased to 0.5 ± 0.97 ($P<0.05$), and at night 0 ($P<0.05$). By scale TSS to 0.1 ± 0.32 ($P<0.05$), on a scale of NSS to 0.2 ± 0.63 ($P<0.05$), by NDS scale total score to 5.1 ± 2.96 ($P<0.05$).

According to the results EMG marked improvement M-response amplitude (mV): n.peroneus (right 4.13 ± 2.23, left 5.18 ± 4.61) and n.tibialis (right 7.4 ± 4.36; left 8 ± 3.86 ($P<0.05$)), the speed of nerve impulse increased (m\s): n.peroneus ((right 67.4 ± 11.7; left 64.9 ± 13)) ($P<0.05$), n.tibialis (right 52.6 ± 14.7 ($P<0.05$); left 44.8 ± 18.9), in Group 2.

Conclusions

i) The using injectable form of Milgamma then assigning Milgamma pills leads to the improvement of both subjective and objective criteria DSPN, but the effect of treatment is not preserved after its termination within 2 months of observation. ii) The using Milgamma Mono maintains the therapeutic effect among the patients with DSPN after 2 months of reception.

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P426

Association of angiotensin-converting enzyme gene I/D polymorphism and aldosterone synthase (*CYP11B2*) gene −344T/C polymorphism with the risk of nephropathy in diabetic patients

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Introduction

Diabetic nephropathy (DN) is one of the most serious chronic complications of diabetes mellitus characterized by persistent albuminuria, raised arterial blood pressure, a lowered glomerular filtration rate, and high-risk of cardiovascular morbidity and mortality. The vascular genes (Angiotensin-converting enzyme) *ACE*, and (aldosterone synthase) CYP11B2 are involved in alterations in vascular endothelium, and are suggested to play a role in the susceptibility of diabetic nephropathy. The aim of our study was to find out the role of ACE (I/D) and CYP11B2 −344C/T polymorphisms in genetic susceptibility of diabetic nephropathy in Belarusian population.

Methods

A total of 59 cases with diabetes types 1 and 2 and 16 control subjects were enrolled for our study. We divided all patients into three groups: 16 normal controls, 31 without DN, and 21 with DN. DNA was isolated from peripheral blood leucocytes, and genotyped using allele specific PCR (ACE I/D) or PCR (CYP11B2) methods.

Results

Genotype frequencies of the ACE (I/D) polymorphysm were in accordance with the Hardy–Weinberg equilibrium. In subjects with DN, the frequencies of the DD, ID and II genotypes were 0.293, 0.373, and 0.320 respectively. The allelic frequency of the D and I allele in the nephropathy group was 0.523 and 0.386 and 0.594 and 0.406 in the control group.

We found no significant association of the ACE I/D and CYP11B2 −344C/T polymorphism with DN in genotype, allele, dominant, and recessive models.

Conclusion

Our preliminary data did not reveal significant association of the ACE I/D and CYP11B2 −344C/T polymorphism with nephropathy in patients with diabetes. However, more investigations are required to further this association.

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P427

Sclerostin distribution in children and adolescents with type 1 diabetes mellitus and correlation with bone metabolism markers and bone mineral density

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Introduction

Sclerostin is an inhibitor of the Wnt/β-catenin bone metabolic pathway. Increased sclerostin levels and reduced bone mineral density (BMD) have been documented in adult patients with diabetes mellitus (DM), predominantly in those with type 2 diabetes mellitus (T2DM). No relevant data exist on childhood T1DM. Our aim was to study plasma sclerostin concentration in children and adolescents with T1DM and controls and to correlate sclerostin levels with metabolic bone markers and BMD.

Materials and methods

Forty children and adolescents with T1DM were evaluated (mean$\pm$S.D., age: 13.04 ± 3.53 years, T1DM duration: 5.15 ± 3.33 years), along with 40 healthy matched controls (mean$\pm$S.D., age 12.99 ± 3.3 years). Sclerostin, osteocalcin, C-telopeptide crosslinks-CTX, electrolytes, PTH, total 25(OH)D, and total body BMD were measured.

Results

Sclerostin levels demonstrated a Gaussian distribution (Shapiro–Wilk $z=-1.685$, $P=0.95$, kurtosis$=2.77$, skewness$=0.13$), with no significant difference between patients and controls (51.56 ± 12.05 vs 50.98 ± 13.55 pmol/l, $P=0.84$). Lower values were found in girls (49.1 ± 12.7 vs 53.9 ± 12.3 pmol/l, $P=0.05$) and in prepubertal children (47.3 ± 11.6 vs 53.3 ± 12.9 pmol/l, $P=0.02$). Sclerostin values significantly and gradually increased in children through pubertal Tanner stages 1–3, then reduced in stage 4 adolescents and increased again in pubertal stage 5 adolescents (ANOVA $F=4.56$, $P=0.0024$). Sclerostin levels were positively correlated with logCTX ($r=0.41$, $P<0.001$), logOsteocalcin ($r=0.33$, $P=0.004$), total body BMD ($r=0.34$, $P=0.0018$), and BMD *Z*-score ($r=0.27$, $P=0.015$).

Conclusions

T1DM children and adolescents had similar levels of sclerostin with controls. Sclerostin was correlated with both resorption and formation markers and also with bone mass indices, gender and pubertal stage. The decrease in sclerostin values observed in pubertal stage 4 adolescents coincides with the concurrent growth spurt, and is consistent with sclerostin physiology as an inhibiting signal.

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P428

Higher levels of osteoprotegerin and S-RANKL in children and adolescents with type 1 diabetes mellitus may indicate increased osteoclast activity and predisposition to lower bone mass

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Introduction
Diabetes mellitus (DM) is a risk factor for reduced bone mass. Several bone metabolic pathways seem to be disrupted in patients with type 1 diabetes mellitus (T1DM).
Materials and methods
We evaluated 40 children and adolescents with T1DM (mean ± s.d., age 13.04 ± 3.53 years, mean ± s.d., T1DM duration 5.15 ± 3.33 years) and 40 healthy age- and gender-matched controls (mean ± s.d., age 12.99 ± 3.3 years). Osteoprotegerin (OPG), receptor activator of nuclear factor-κB ligand (s-RANKL), osteocalcin, C-telopeptide crosslinks-CTX, electrolytes, PTH, total 25(OH)D were measured and total body bone mineral density (BMD) was evaluated with dual energy X-ray absorptiometry (DXA).
Results
Patients had significantly higher levels of OPG (6.15 ± 1.56 vs 5.01 ± 1.5 pmol/l, $P<0.001$) and s-RANKL (logS-RANKL 5.97 ± 0.63 vs 5.51 ± 0.84, $P=0.004$). Patients also had lower levels of PTH (logPTH 3.25 ± 0.52 vs 3.43 ± 0.33, $P=0.036$) and magnesium (1.88 ± 0.12 vs 2.03 ± 0.12 mg/dl, $P<0.001$) and higher levels of ALP (√ALP 14.07 ± 4.13 vs 12.6 ± 3.24, $P=0.05$). Patients and controls had comparable 25(OH)vitD levels, while one third of both groups had low 25(OH)vitD levels (<20 ng/ml). Osteocalcin was highly correlated with CTX in both groups ($r=0.75$, $P<0.001$), indicating coupling of bone resorption and formation. OPG and s-RANKL were associated in controls ($R^2=0.15$, $P=0.021$) but not in patients ($R^2=0.006$, $P=0.64$), possibly indicating an osteoclastic disorder. Bone formation was not significantly affected. BMD had greater variance in patients. Furthermore, longer T1DM duration was associated with lower BMD *Z*-scores ($r=-0.41$, $P=0.009$).
Conclusion
RANKL/OPG axis seems to be significantly activated in patients with T1DM. These changes could indicate abnormal osteoclast function and could be associated with the lower bone mass, found in patients with longer disease duration.

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P429

The association of peripheral artery disease with renal function and albuminuria in diabetic patients

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Objective
The association between albuminuria and peripheral artery disease (PAD) could be confounded by renal function. Albuminuria reflects generalized disruption of endothelial cell function. This study was conducted to examine the association of PAD with low glomerular filtration rate (GFR) and albuminuria in diabetic patients.
Methods
A total of 254 diabetic patients were included. We examined the age, sex, duration of diabetes, GFR, urinary albumin, high-sensitivity C–reactive protein (hsCRP), and presence of hypertension, dyslipidemia, coronary artery disease, stroke, and PAD. Patients with estimated GFR <60 ml/min per 1.73 m^2 were classified as having chronic kidney disease (CKD). Urinary albumin was measured using urine albumin:creatinine ratio (ACR) and albuminuria was defined as microalbuminuria (ACR, ≥30 and <300 mg/g) and proteinuria (ACR, ≥300 mg/g).
Results
When stratified by the presence of CKD, there were statistical differences in age (normal vs CKD, 60.48 vs 65.16 years), sex (female, 37.6 vs 52.6%), duration of diabetes (8.44 vs 14.78 years), urinary albumin (no albuminuria/microalbuminuria/proteinuria, 37.4/42.7/19.9 vs 15.8/36.0/48.0%), and presence of hypertension (59.6 vs 84.2%), dyslipidemia (60.1 vs 75.0%), and stroke (15.7 vs 32.9%). There was no difference of PAD in patients with and without CKD. When stratified by the urinary albumin, there were statistical differences in presence of hypertension (no albuminuria/microalbuminuria/proteinuria, 52.6/65.0/88.6%), CKD (15.8/27.0/51.4%), and PAD (7.9/19.0/27.1%). When stratified by the presence of PAD, there were statistical differences in age, sex, duration of diabetes, urinary albumin, hsCRP, and presence of hypertension and CAD. There were no statistical differences in the CKD and presence of stroke in patients with and without PAD.
Conclusion
These results suggest that PAD in diabetic patient is more associated with albuminuria than renal function, and hsCRP might be used in diagnosis or screening of PAD in diabetic patients.

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P430

Low FT_4 syndrome in gestational diabetes

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About 7% of pregnancies are complicated by diabetes, out of which 97.5% gestational diabetes (GMD), 2.5% pre-gestational diabetes. We investigated 29 women at their first pregnancy who had GMD medium risk factor in the absence of pre-existing thyroid pathologies. We divided them in two groups: the first 19 women (age 33.9 years) resulted affected by GMD (OGTT effected, according to Carpenter and C criteria), between pregnancy weeks 24–28; the second ten women (age 34.3 years) showed a normal OGTT (control group). In all the patients the thyroid hormones were investigated. Normal mean values of FT_3 and TSH, negative TPO and low mean values of FT_4 0.8 (0.71–1.85 ng/dl) have been evidenced in the first group. In the control group the mean value of FT_4 was 1.04. During the pregnancy the low values of FT_4 are normally due to a reduced iodine intake (mild thyroid failure) which may have possible effects on the fetal neurological system. In the first group, 11 patients, had been using iodized salt for more than 2 years (mean FT_4 0.80 ng/dl), in the second group, eight patients, had never been using it (mean FT_4 0.78 ng/dl); in the control group, five patients had been using iodized salt (mean FT_4 1.1), and five had not (mean FT_4 0.9). In the GMD the sole use of the iodized salt is not sufficient to keep the FT_4 levels in the normal range and it is furthermore assumable that the insulin resistance may stimulate the inhibitor of the serum binding of thyroid hormones like the free fatty acids.

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P431

Metabolic syndrome and cardiovascular risk are less prevalent in LADA vs type 2 diabetes patients

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Background
Latent autoimmune diabetes in adults (LADA) is a form of autoimmune diabetes with features overlapping types 1 and 2 diabetes mellitus (T2DM). Frequently patients with LADA could be confound with T2DM patients if it was not performed a glutamic acid decarboxilase antibodies (GADA) evaluation. Even thou LADA and T2DM have similar phenotype, patients with LADA seem to have less frequent macrovascular complications.
The aim of the study was to compare prevalence of risk factors and metabolic syndrome in LADA vs T2DM patients.

Material and methods
From 798 patients with DM, using a clinical tool based on age at onset (>30 years old), no need of insulin 6 months at onset, actual treatment with insulin, we selected 234 patients. According GADA positivity, 104 patients (57 females) were positive (LADA) and 130 patients (68 females) were negative (T2DM). Clinical and laboratory data were obtained: weight, blood pressure, total cholesterol, triglycerides, and HDL-cholesterol. Presence of metabolic syndrome (MetS) was evaluated according NCEP/ATP III criteria.
Results
LADA patients were younger than T2DM and we made adjustment for age. Triglycerides were 168.25±113.10 mg/dl in LADA vs 188.5±108.2 mg/dl in T2DM ($P=0.024$), HDL-cholesterol was 47.78±14.34 mg/dl in LADA vs 40.3±19.78 mg/dl ($P=0.001$), total cholesterol was 203.27±55.52 mg/dl in LADA vs 220.84±54.4 mg/dl (0.025), systolic blood pressure was 133.7±24.35 mmHg in LADA vs 141.44±20.67 mmHg ($P=0.009$), diastolic blood pressure was 76.68±14.3 mmHg in LADA vs 85.2±11.6 mmHg ($P=0.03$), and prevalence of MetS was 59.6% in LADA vs 88.4% in T2DM ($P<0.001$).
Conclusions
LADA patients had a better metabolic profile than T2DM patients with lower triglycerides, total cholesterol, systolic and diastolic blood pressure, and higher HDL cholesterol and lower prevalence of MetS.

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P432

Erectile dysfunction scores are lower in type 2 diabetes mellitus but not correlate with carotis intima media ticknes or coronary arter disease

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Aim
To evaluate prevalence of erectile dysfunction (ED) in patients with type 2 diabetes in relation to the cardiovascular risk factors.
Methods
A total of 116 males including type 2 diabetic patients ($n=68$, mean age: 56.7 (5.8) years) and age-matched healthy controls ($n=48$, mean age: 57.0 (6.6) years) were included to study. Concomitant hypertension, hyperlipidemia, and coronary artery disease (CAD) were recorded in each subject along with measurement of carotid artery intima–media thickness (CIMT) and evaluation of ED via International Index of Erectile Function (IIEF-5) questionnaire.
Results
Patient and control groups were similar in terms of percentage patients with concomitant hypertension (42.6 and 25.0%), hyperlipidemia (51.5 and 39.6%), and CAD (33.8 and 22.9%) while CIMT measurement (mm) revealed significantly higher values for patients with type 2 diabetes mellitus than controls ($P=0.020$). ED was determined in 75.0% of diabetic patients and in 60.4% of controls with identification of severe ED in 29.4% of overall patient population and 39.2% of patients with ED, whereas only in 10.4% of controls. ED scores was significantly lower in patients than controls (14.3 (7.3) vs 18.2 (6.3), $P=0.004$) with significantly higher percentage of patients than controls in the category of severe dysfunction (29.4 vs 10.4%, $P=0.014$). No significant relation of hypertension, hyperlipidemia, CAD and CIMT to ED was noted.
Conclusion
ED skores are lower in type 2 diabetes mellitus but not correlate with carotis intima media ticknes or coronary arter disease. ED is not suitable for describing cardiovascular risk in type 2 diabetic patients.

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P433

Diabetic polyneuropathy as the only diabetes related complication associated with higher likelihood and more severe forms of erectile dysfunction in type 2 diabetes

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Aim
Erectile dysfunction (ED) has been reported to occur more commonly in diabetes than general population with the prevalence rate varies widely from 35 to 75%. Patients with diabetes was also shown to have much earlier onset of ED and more severe form of the disease associated with a poorer quality of life. We aimed to evaluate association of ED with diabetes related complications in patients with type 2 diabetes in our study.
Methods
In a total of 68 type 2 diabetic patients males (mean age: 56.7 (5.8) years), polyneuropathy, nephropathy, and retinopathy were assessed based on medical history, physical examination, and laboratory findings. ED was evaluated via application of the five question of International Index of Erectile Function (IIEF-5) questionnaire via face to face interview method. The severity of sexual dysfunction was classified into five categories (i.e. severe 5–7, moderate 8–11, mild to moderate 12–16, mild 17–21, and no ED 21–25).
Results
Mean (S.D.) duration of diabetes mellitus was 7.4 (6.9) years and mean HbA1c was 8.6 (2.0) in patients. Polyneuropathy was noted in 46.2% of patients, nephropathy in 30.8% and retinopathy in 33.8%. ED was determined in 75.0% of diabetic patients and severe ED in 29.4%. Univariate analysis revealed that diabetic polyneuropathy was the only significant factor associated with higher likelihood (93.3% in the presence and 60.0% in the absence of neuropathy) and severity (43.3% in the presence and 14.3% in the absence of neuropathy) of ED ($P=0.004$).
Conclusion
In conclusion, findings from the present cross sectional single centre study revealed diabetic polyneuropathy as the only diabetes related complication associated with higher likelihood and more severe forms of ED. In patients with diabetic polyneuropathy, ED should be evaluated.

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P434

The influence of maternal BMI and weight gain in gestational diabetes: results of the Portuguese population in 2011

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Background and aims
Maternal BMI and weight gain are associated with maternal and fetal complications in gestational diabetes (GD), but their relative contribution is not clearly defined. Our aim was to determine the influence of BMI and weight gain in the evolution of GD.
Material and methods
Multicenter, retrospective study of women diagnosed with GD at the medical centers of the Portuguese Group for the Study of Diabetes and Pregnancy in 2011. We used the diagnostic criteria of the International Association of Diabetes and Pregnancy Study Groups and excluded multiple pregnancies and cases with lack of information about maternal BMI. The χ^2, Mann–Whitney *U*, Kruskall–Wallis, and one-way ANOVA tests were used for statistical analysis.
Results
We included 1577 patients, with mean age 33.1±5.3 years. Sixty percent were overweight/obese and 38.7% were treated with insulin. The mean weight gain in pregnancy was 9.9±5.5 kg and 27.9% had an excessive weight gain for their BMI. Maternal BMI was associated with multiparity ($P<0.001$), previous GD ($P=0.005$), previous fetal macrosomia ($P<0.001$), treatment with insulin ($P<0.001$), and excessive weight gain ($P<0.001$). Compared with women with normal BMI, obese women were diagnosed ($P<0.001$) and started insulin therapy ($P=0.007$) earlier, were treated with higher insulin dose ($P<0.001$), had higher mean HbA1c in the third trimester ($P<0.001$), heavier newborns ($P<0.001$) and had a smaller absolute weight increase ($P<0.001$). Women

with excessive weight gain were younger ($P=0.003$), had a later diagnosis ($P<0.001$), needed higher insulin dose ($P=0.009$), had higher HbA1c in the third trimester ($P<0.001$) and gave birth to heavier newborns ($P<0.001$).
Conclusion
In our population, women with higher BMI and those with excessive weight gain had a more severe GD evolution and might need a more intensive treatment approach.

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P435

Hemostatic biomarkers in selected group of patients with type 1 diabetes: are they associated with different degrees of diabetic retinopathy

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Background
Diabetic retinopathy (DR) is the leading cause of blindness in the world. Retinopathy and nephropathy can still progress in diabetics despite optimal metabolic control. The aim of the present study was to determine whether different degrees of DR (proliferative or non-proliferative) were associated with abnormally modulated hemostatic parameters in patients with type 1 DM.
Method
52 type 1 diabetic patients and 40 healthy controls were enrolled in the study. Patients were then subdivided into three categories. Group I was defined as those without retinopathy, Group II with NPRP, and Group III with PRP. We have compared these subgroups with each other and the control group (Group IV) according to the serum fibrinogen, plasminogen, α2-anti-plasmin, and PAI.
Results
We detected that PAI-1 levels were higher in the diabetic groups than control, but this was not statistically significant whereas serum fibrinogen ($P=0.224$) and plasminogen ($P=0.224$) were similar between the diabetic and control groups. α-2-Anti-plasmin in Groups I, II, and III was higher compared to the control group ($P<0.01$, $P<0.05$, and $P<0.001$ respectively) and the positive correlation identified between serum α2-anti-plasmin and HbA1c levels ($r=0.268$, $P=0.031$).
Conclusion
To our knowledge there are only a small number of studies measuring α2-antiplasmin levels in type 1 diabetes. A positive correlation between α2-anti-plasmin with HbA1c suggests that fibrinolytic markers may improve with disease regulation, and better glycemic control. High α2-anti-plasmin level might be a novel a risk factor for development of DR. Confirmation of these data would allow a better understanding of the pathogenesis of DR.

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P436

Markers of endothelial dysfunction in type 1 diabetics with or without microalbuminuria

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Introduction
Diabetic nephropathy (DN) is an important one of the complications and is detected in almost 30-40% of the patients with type 1 diabetes mellitus (T1DM). Besides the well known risk factors, endothelial dysfunction also plays a role in the pathogenesis of DN and diabetic retinopathy. Our aim was to determine flow mediated dilation measurements and serum soluable ET-1, ICAM-1, and VCAM-1 levels in T1DM patients with or without inceased albumin excretion and compare them with the control group.
Methods
We enrolled 73 patients with T1DM. Diabetic patients were divided into two subgroups according to microalbumin measurements in 24 h urine collections. Patients with microalbuminuria formed Group 1 and without microalbuminuria were defined as Group 2. We have also enrolled 40 subjets with similar sex and age distrubution as control group (Group 3). Serum ET-1, ICAM-1, and VCAM-1 levels were determined and FMD measurements were done in all individuals.
Results
Mean age, sex distrubition, presence of hypertension, serum LDL, and triglyceride levels were similar in all groups. Diabetic groups were similar in regard to glycemic control and disease duration. Mean FMD measurement was lower in diabetic groups compared to the control group. FMD was negatively correlated with age. We didn't detect any difference between groups according to serum ET-1 levels. Median serum ICAM-1 level was higher in diabetic groups compared to the control group. Median serum VCAM-1 level was higher in the group of patients with microalbuimuria compared to the normoalbuinuric and control groups. Serum VCAM-1 level was found to be posively correlated with degree of urinary albumin excretion ($P>0.001$).
Conclusion
ICAM-1 and VCAM-1 are proinflammatory molecules that play an important role in pathogenesis of endothelial dysfunction. VCAM1 may be used as a predictive marker for risk stratification of nephropathy development and progression in T1DM.

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P437

Skin findings among diabetic patients

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Aim
Diabetes mellitus affects many systems and one of them is skin. Skin findings among diabetic patients reported 30–71%. Skin findings may be due to direct metabolic effects of diabetes but complications and drugs may be cause as well. In this study our aim was to investigate the skin findings and prevalence among diabetic patients that admitted to endocrinology policlinic.
Method
81 patients involved to study, skin examination of the patients were performed by an dermatologist and skin changes were recorded. Patient's demographic data, blood glucose, HbA1c, lipid parameters, and complications were recorded as well. Patients that had previous dermatologic diseases were excluded.
Findings
81 patients were evaluated in terms of skin findings, seven of them were type 1 DM (8.6%), 74 of them were type 2 DM (91.4%), 28 patients (34.6%) were males and 53 patients (65.4%) were females. Most common skin changes was acrochordon ($n=49$, 61%), and second common finding was diabetic thick skin ($n=44$, 54.9%). Other findings were as follow; pruritus and dryness in 42 patients (52.4%), periungual telangiectasias in 35 patients (43.9%), diabetic dermopathy in 28 patients (35.4%) and other findings in seven patients (9.5%).When we evaluate the association of skin changes and antidiyabetic drugs, diabetic dermopathy was seen 25% of metformin using type 2 DM patients but 47% of non-metformin using type 2 DM patients and this association is statistically significant ($P<0.05$). Acrochordon was seen 46% of insulin using type 2 DM patients, but 75% of non-insulin using type 2 DM patients and this finding is statistically significant ($P<0.05$).
Conclusion
Skin changes in diabetes frequently occur after diabetes diagnosis but sometimes this changes may be the initial finding. In type 1 DM most common findings are autoimmune skin changes whereas in type 2 DM infection associated skin findings are most common. In our study one of the important findings is lower diabetic dermopathy frequency among metformin using patients. Diabetic patients should be screened for diabetic skin changes with other chronic complications.

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P438

Vascular endothelial growth factor polymorphism +405 G/C is associated with early stage of diabetic nephropathy in patients with type 2 diabetes

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Background
One of the basic genetic factors that impact on development of diabetic nephropathy is enhanced expression of vascular endothelial growth factor (VEGF).
Objective
To study association between VEGF polymorphism +405 G/C and early stage of chronic kidney disease (CKD) in patients with impaired glycemic states.
Materials and methods
73 included patients were divided into three groups: group 1–26 patients with prediabetes (impaired fasting glucose and impaired glucose tolerance), group 2–28 patients with type 2 diabetes (T2D) and group 3–20 almost healthy person. To determine the stage of CKD we calculated glomerular filtration rate (GFR; ml/min per 1.73 m^2) by Cockcroft–Gault equation. Patients with CKD3–5 were excluded. We estimated distribution of VEGF genotype in study groups.
Results and discussion
Distribution of VEGF genotype and CKD stage are presented in Table 1.
We revealed that VEGF +405 G/C polymorphism in patients with T2D was associated with decreased GFR (CKD2): 84.28 (82.59; 87.38) compared to 106.07 (89.63; 136.91) in control group ($P=0.02$). We didn't reveal statistical significance in groups with VEGF polymorphism C/C and G/G. It can be assumed that polymorphism C/C and G/G possess nephroprotective action. Increased glucose levels promote activation of VEGF +405 G/C polymorphism.
Conclusion
VEGF +405 G/C polymorphism was associated with Stage of CKD in patients with T2D and was not associated with GFR impairment in patients with prediabetes.

Table 1 Distribution of VEGF genotype and CKD stage in study groups

	Group 1 ($n=26$)		**Group 2** ($n=28$)		**Group 3** ($n=19$)	
	CKD1 (n)	CKD2 (n)	CKD1 (n)	CKD2 (n)	CKD1 (n)	CKD2 (n)
G/C	4*	3*	3	11	6	2
C/C	2*	4*	1*	–	1	–
G/G	13*	–	10*	3*	10	–

*Differences are not statistically significant.

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P439

Analysis of ultrasound structure of the thyroid gland and assessment of structural changes in patients with diabetes mellitus type 1 at different stages of chronic kidney disease

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Existing data on the anatomical state of the thyroid gland (ThG) in patients with chronic kidney disease (CKD) are contradictory.
Objective
The aim was to analyze the anatomical features of the ThG and their correlation if it exists in patients with diabetes mellitus type 1 (T1DM) at different stages of comorbid CKD.
Materials and methods
We recruited 53 patients (17 m; 36 f; age 43.7±11.3 years; BMI 25.8±5.0 kg/m^2; duration of T1DM 22.2±7.5 years; age at onset of impairment of renal function 34.5±11.2 years; duration of GFR decline 8.8±6.7 years) estimated by using MDRD formula at CKD stages 1 ($n=6$), 2 ($n=25$), 3 ($n=19$), 4 ($n=1$), and 5D ($n=2$). All patients underwent thyroid ultrasound with the assessment of following parameters: total volume of the ThG, echostructure (homogenous, and heterogenous), vascularization (expressed, and moderate), hyperechoic cords (absence, expressed, and moderate), echodensity (normal, increased, and decreased), and presence of local and any structural pathology. Revealed changes in the structure of the thyroid gland were analyzed. Nonparametrics and descriptive statistical methods were used.
Results
Comparative analysis of patients in the subgroups according to CKD stages didn't reveal any reliable differences in the assessed parameters. We found significant correlation of hyperechoic cords ($r=0.286$; $P<0.05$), echodensity ($r=0.294$; $P<0.05$) and duration of GFR decline. Total volume of thyroid gland correlates with echodensity ($r=-0.387$; $P<0.05$). Analysis of ultrasound data showed the presence of deviation from the normal structure of ThG in 41 (77.36%) and local pathology in 21 patients (39.62%) respectively.
Conclusion
The obtained data are controversial and require further detailed in-depth study. These results do not allow us to judge of the existing of relationship between structural changes of the thyroid gland and the presence of CKD.

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P440

Comparative analysis of methods for the evaluation of renal function in patients with diabetes mellitus type 1 at different stages of chronic kidney disease

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The aim was to analyze the efficiency of various methods of examination to update the degree of diabetic nephropathy and to determine the optimal to predict the decline in renal function in patients with diabetes mellitus type 1 (T1DM).
We examined 50 patients (17 m; 33 f; age 40.1±11.7 years; BMI 25.9±5.0 kg/m^2; duration of T1DM 22.3±8.1 years; and age at T1DM onset 21.6±13.2 years) at chronic kidney disease (CKD) stages 1, 2, 3 ($n=22$; 18; and 10 respectively). GFR was estimated using Cockcroft–Gault (CG) and MDRD formulas. Urinary protein excretion in the morning and daily samples, urine albumin:creatinine ratio (ACR), endogenous creatinine clearance (CrCl), serum creatinine levels (sCr) were measured.
Comparative analysis of patients in the subgroups according to CKD stages revealed reliable differences in protein excretion in the morning urine sample (0.160 g/l, 95% CI 0.081–0.240, $P=0.047$). Assessing the level of urinary albumin excretion, ACR, the urinary protein excretion in the daily sample no differences have been received. eGFR using CG and MDRD formulas strongly correlates with endogenous CrCl based GFR ($r=0.717$; 0.614 respectively).
Urinary protein excretion in the morning sample correlates with GFR ($r=0.393$), urinary daily protein excretion ($r=0.916$), sCr ($r=0.470$), eGFR CG ($r=-0.398$), and CKD stage ($r=0.417$). At the same time the urinary daily protein excretion correlates only with sCr ($r=0.527$). ACR correlates with the age at T1DM onset ($r=-0.334$).
We can assume that urinary protein excretion in the morning sample which is rather cheap, simple and convenient for patients in compare with such reliable and accurate methods as the evaluation of daily urinary protein excretion and ACR can be an efficient method of predicting the decline in renal function in patients with T1DM at CKD stages 1–3. The obtained data confirm that the use of CG formula to estimate GFR is preferable in patients with earlier stages of CKD.

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P441

QT intervals and vitamin D levels in diabetic patients

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Objective
Diabetes is an independent risk factor for sudden cardiac death. Prolongation of the QT interval on the ECG increases the risk of arrhytmias and sudden death, and the increased prevalance of QT prolongation is an independent risk factor for cardiovascular death in diabetic patients. Low vitamin D levels are also associated with cardiovascular mortality. The aim of this study was to investigte the relationship between QT interval and vitamin D levels in type 2 diabetic patients.

Materials and method
One hundred and thirty type 2 diabetic patients (62 females and 68 males, mean age: 62.17±7.15 S.D. years) and fourty five age matched healthy volunteers (23 females, and 22 males, mean age: 60.97±5.67 S.D. years), for control group included in this study. Diabetic patients were classified in two groups according to HbA1c levels. Group 1 (HbA1c<6.5) Group 2 (HbA1c<6.5). In the ECG recordings, QT duration, corrected QT duration (QTc) and corected QT dispersions (QTd) were measured. 25 hydroxyvitamin D levels, calcium, phosphors, and blood glucose levels determined in all groups.
Results
Diabetic patients had significantly longer QTc than the control group ($P=0.02$). QTd was similar in diabetic and control group. However in diabetic cohort QTd was longer in group 1 patients ($P=0.04$). Diabetic patients with low vitamin D levels have longer QTc time ($P=0.07$). Fasting glucose levels and HbA1c levels were inversely corralated with vitamin D levels ($P=0.03$, $r=-0.16$ and $P=0.03$, $r=-0.18$ respectively). vitamin D levels were also inversely corralated with QTc ($P=0.02$, $r=-0.17$).
Conclusion
QTd prolonges in diabetic patients. Low levels of vitamin D increases this prolongation.

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P442

Dental care and periodontal disease in Turkish diabetic patients

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Diabetes mellitus is a common and growing global health problem leading to several complications. Among these, periodontal diseases are considered as the sixth complication of diabetes. The goals of this cross-sectional study were to assess Turkish diabetic patients' oral health behaviors and association with demographic characteristics, access to dental care and need for improved health education. The study sample consisted of 121 diabetic patients (43 M/78 F), with a mean age of 49.8±13.3 years. At baseline, all patients completed self-administered questionnaires to evaluate oral hygiene habits and underwent a thorough dental/periodontal examination. 68.0% of diabetic patients noted not going to regular dental examinations, admitted to the dentist only when in pain. 74.6% of patients were not informed by an endocrinologist that they are susceptible to developing periodontitis. The mean number of decayed, missing, filled teeth index (DMFT) was 12.09±7.09. No significant gender difference was evident in the periodontal status. Mean A1c levels of the patients was 7.68±1.76%. Initial data in diabetics with A1c level higher than 7.0% shows an increase in probing pocket depth and clinical attachment loss ($P=0.039$ and $P=0.005$ respectively). Diabetics who knew their last measured A1c had a decrease of the missing teeth number and not an increase in probing pocket depth. Diabetic patients with comorbidities had a significantly greater prevalence of missing teeth (80.0%) and high plaque index (80.0%) as compared to patients without comorbidities ($P=0.026$ and $P=0.029$ respectively). A significant decrease in the severity of periodontal disease was found with escalating levels of education. The non-smokers had a significantly better oral hygiene than the current smoker. The results of this study suggest that inadequate glycemic control may predict the breakdown of periodontal tissue in diabetic patients. Our results also support that oral health of diabetic patients should be improved in order to avoid adverse outcomes.

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P443

Clinical profile and management of diabetic osteoarthropathy

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Introduction
The diabetic foot osteoarthropathy is defined as a progressive painless arthropathy of one or more joints due to an underlying neurological injury. It is the bed of complications and severe foot infections and involves the functional prognosis. Through observations of patients we report the difficulty of management of wounds on foot osteoarthropathy.
Observation
It is five diabetic patients hospitalized in our department with an array of severe infection of the feet on Charcot foot. All patients with longstanding diabetes at the stage of microvascular complications, severe peripheral neuropathy was present in all cases. Clinical examination revealed deformities type Charcot foot associated with infected wounds, signs of frank infection, and inflammation. Bone involvement was frequent. The treatment consisted on: discharge, antibiotics and surgical debridement in some cases. The surgical treatment was conservative and was limited to a toe amputation. The average hospital stay is 45 days.
Discussion
The Charcot osteoarthropathy is a serious complication of diabetic neuropathy. The diagnosis is often delayed at the stage of final major deformations on which are grafted trophic disorders, recurrent severe infections, and osteomyelitis. Its management is cumbersome and costly. However, only an early diagnosis followed by prompt intervention may limit the progression to foot deformities, or amputation.

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P444

Comparative assessment of parathyroid hormone and bone turnover markers in diabetic and non-diabetic patients with end-stage chronic kidney disease

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It's well known that secondary hyperparathyroidism (SHPT) is common in patients with chronic kidney disease stage 5 (CKD5D), on dialysis. The aim of our study was to analyze peculiarities of SHPT in diabetic patients in comparison to those with other course of CKD5D.
We studied 25 diabetic and 180 non-diabetic patients with CKD5D, mean age 47.5±10.8 years; age at dialysis onset 42.7±11.7 years; dialysis duration 4.7±3.9 years. Groups were matched for age, gender age at dialysis onset and dialysis duration. We measured serum levels of intact parathyroid hormone (iPTH), N-terminal mid-fragment osteocalcin (N-Mid-OC), C-terminal telopeptide of type I collagen (β-CTx), total calcium (Ca), phosphates (P), alkaline phosphotase in both groups by immunoassay.
Median level of iPTH was significantly lower in diabetic patients than in non-diabetic (97.2 vs 245.5 pg/ml; $P=0.001$). Prevalence of secondary hyperparathyroidism was significantly lower in diabetic patients (12.0 vs 47.8%; $P=0.0004$) while frequency of normal uremic iPTH level (150–300 pg/ml) and low iPTH level was higher in diabetic patients (28.0 vs 11.7%; $P=0.035$ and 60.0 vs 40.6%; $P=0.05$ respectively). Analysis of biochemical markers of bone metabolism shown that N-Mid-OC and β-CTx are significantly lower in diabetic group: 194.6 vs 331.5 ng/ml, $P=0.02$ and 1.69 vs 1.98 ng/ml, $P=0.05$ respectively. Serum level of phosphates was the same in both groups, at the same time serum calcium was significantly lower in diabetic patients (2.17±0.27 vs 2.47±0.33; $P=0.0001$).
We can assume that diabetic patients with CKD5D are at lower risk of developing SHPT than patients with other course of CKD5D. Our data allows suggesting that diabetic patients on dialysis are at greater risk of low-turnover bone disease. Further study is required to develop differentiated approach for diagnostics and treatment of parathyroid function abnormality and associated mineral and bone disorders in diabetic patients with CKD5D.

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P445

Autoimmune pancreatitis after intravenous insulin desensitization in a diabetic patient allergic to insulin without pancreatic reserve

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Introduction
Allergy is an uncommon side-effect of insulin treatment in which desensitization represents an alternative when initial approaches are not effective. Autoimmune pancreatitis (AIP) is an even more rare disease that generally has a successful

response to corticosteroids. The case of a 50-year-old diabetic man who developed both processes sequentially is presented.
Case report
The patient was admitted for acute diabetes mellitus (DM) decompensation after abandonment of Aspart/Protamine. He developed severe urticaria, dyspnea, and facial angioedema in every successive treatment with Aspart, Lispro, and regular insulin with partial response and reappearance after antihistamines and/or corticosteroids. Along with low levels of basal and stimulated C-peptide; organ-specific antibodies, total and specific IgE were negative; however intradermal test with insulin was positive. Therefore, the patient underwent a protocol for fast intravenous desensitization. Although infusion of others had to be suspended, desensitization with Lispro was effective. He was discharged controlled with subcutaneal Lispro and Lispro/Protamine. Three weeks later, he presented abdominal pain, jaundice, choluria and fever; along with a serum cholestatic pattern, hyperbilirubinemia, lymphocytosis, and PCR elevation. Imaging showed diffuse pancreatic enlargement with delayed enhancement and peripancreatic adenopathies. Biliopancreatic catheterization achieved clinical/analytical improvement. ERCP evinced Wirsung duct irregular narrowing. Ecoendoscopy guided FNA could not obtain sufficient material. Serum total IgG and IgG4 were elevated. Oral prednisone 40 mg/day was maintained for 3 weeks with an afterwards gradual decrease. During this time, the patient recovered completely and sustained an adequate glycemic control with less insulin.
Conclusions
Insulin desensitization has been associated with elevation of IgG4 levels. This should be evaluated as a possible association/predisposition/causal relationship where the role of IgG4 can range from just a confounding component, through a simple marker to an etiological/crucial factor. AIP is also associated with corticosteroid-responsive DM due to mechanisms still to be cleared.

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P446

A lepromatous lepra case presented like diabetic foot

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A 67–year-old female patient was transferred to our hospital from a nursing home for high capillary glucose levels and foot ulcer considered as diabetic foot infection. Her past medical history could not be obtained because of mental retardation with unknown etiology and absence of relatives.
A purulent foot ulcer sized 4×3 cm was found in right heel. She also had deformities in her hands, feet, and her nose. Peripheral neuropathy was also detected. Her fasting glucose was 121 mg/dl, her HbA1c was 5.8%. Oral glucose tolerance test revealed impaired glucose tolerance. She also had a stage IV chronic kidney disease with a creatinin clearence of 15 ml/min. Because of her clinical findings related to leprosy we searched all the databases in Turkey. We found a registration for our patient in lepra clinic in Ankara. The lepra basil was not found in the skin biopsy which was interpreted as chronic non-contagious lepromatous lepra.
We started hemodialysis programme for her CKD and advised only diabetic diet. Her infection in the foot was treated with sulbactam-ampicilline and local antibiotics.
Leprosy is a very rare disease with a prevelance rate of 0.0002% in Turkey. Here we present a chronic leprosy case with chronic complications including foot ulcers, which presented like diabetic foot infection.

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P447

Prolonged cerebellar ataxia after: severe hypoglycemic attack in a patient with T1DM: a rare but disturbing sequela

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Introduction
Hypoglycemia is common in people with diabetes who aim to achieve strict glucose control. The neurologic manifestations of hypoglycemia are mostly reversible and includes behavioral changes, difficulty in concentration, confusion, loss of fine motor functions, and seizures. Herein we have presented a case who was pregnant and experienced severe hypoglycemia which led to permanent ataxia.
Case
A 26-years-old female patient was brought to our emergency room by her husband because of being found unconscious. She was 10 weeks of pregnant and had history of T1DM for 13 years. At the time of admission her plasma glucose level was 23 mg/dl. In the initial physical examination she was lethargic, blood pressure was low with tachycardia while body temprature was normal. In the obstetric USG, the fetus was alive. In the labaratory examination, she had normal kidney and liver function tests, electrolytes, thyroid function tests, and vit. B12 levels. After her blood glucose returned to normal, complete neurologic examination was made. Her pupils were reactive, tendon reflexes were normal but she was dysarthric. On the second day, dysarthria continued. We realized she had gait disturbace and on cordination tests she had severe dysmetria in all four limbs (finger to nose and heel to shin). Cranial MRG and EEG didn't reveal any pathology. With short acting anologue and NPH insulin, her blood glucose levels were within the target range but her dysartria and ataxia persisted upon discharge on the 12 th day. One month after discharge, she still had moderate gait disturbance and slow speech in the control visit.
Conclusion
Cerebellar dysfunction is a rare complication of hypoglycemia and may occur in patients with altered cerebellar glucose kinetics.Differential diagnosis involves hematoma, cerebellitis, drug or alcohol ingestion, Wernicke encephalopathy, vit. B12 deficency, and ataxia telengiectasia. Reconsideration of therapy and glycemic targets and supportive therapy is warrented.

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P448

Mean platelet volume in type 2 diabetic patient: is there a relationship between mean platelet volume and diabetic microvasculary complications?

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Aim
Most diabetic patients suffer from vascular thrombotic complications. Alterations in platelet size are associated with atherosclerotic complications in patients with diabetes. The aim of study is to determine the relationship between mean platelet volume (MPV) and microvascular complications in type 2 diabetic patients.
Materials and methods
Seventy-nine type 2 diabetic patients (mean age 51.0±10.8 years and BMI 31.0±5.5 kg/m^2), and 67 healthy control subjects (mean age 48.8±12.0 years and BMI 30.3±7.3 kg/m^2) included in this study. All study group was matched according to age and BMI. Complete blood count analysis was performed by the automatic hematology analyzer Beckman Coulter LH 750 (Beckman Coulter, USA). The platelet count (PC) and MPV were measured. Chronic microvascular complications in diabetic group were researched. Neurological evaluation, fundus examination, and electromyelogrophy were performed. Spot urinary protein levels, HbA1c, C reactive protein, and fibrinogen levels were measured in all study groups. Patients were separated into sub-groups according to nephropathy, neuropathy, and retinopathy. MPV level were analysed again in all sub-groups.
Results
Fourty-four (34.7%) patients had diabetic neuropathy, 33 (26.0%) patients had diabetic neuropathy, and 13 (10.2%) patients had diabetic retinopathy in diabetic group. We determined that mean MPV levels in diabetic group was significantly different from control group (8.6±0.8 and 7.9±0.8 fl, $P<0.001$ respectively). However, no statistically significant differences were found between PC, CRP, and fibrinogen levels. In subgroup analysis, we demonstrated that mean MPV levels in diabetic nephropathy ($P=0.007$) and diabetic neuropathy groups ($P=0.04$) were higher than control subjects.
Conclusions
In our study, MPV level in diabetic patients with nephropathy and neuropathy is more increase than healthy subjects. Elevated MPV levels in patients with type 2 diabetes mellitus may associate with increased cardiovascular complication risk. MPV level can be used as simple accessible parameter to presumption the thrombotic events in diabetic patients.

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P449

Small fibre neuropathy association with increased mortality in patients with chronic kidney disease, with or without diabetes mellitus

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Background and aim
We carried out a prospective 1-year study to examine the association of sudomotor dysfunction with mortality in patients with chronic kidney disease.
Materials and methods
97 patients from dialysis unit (28 with diabetic nephropathy (DN); 37 with nephroangiosclerosis, (NA), 18 with glomerulonephritis (GN), 14 with other conditions (O)); 32 with type 2 DM and creatinine clearance (CrCl) 30–50 ml/min; and 24 transplanted patients with CrCl > 30 ml/min (of these eight had DM). Neuropathy was documented using the Neuropathy Disability Score (NDS) and the Neuropad® test. Peripheral vascular disease (PAD) was diagnosed by CW Doppler. Investigations were performed twice: 1 and 2 years ago.
Results
Among DM patients, 13 exhibited diabetic foot pathology, one patient with critical ischaemia in the NA group and 1 in the GN group. 14 patients on haemodialysis had died: 9 in the NA group (mean age 66.8 ± 11 years), four among DM (mean age 59 ± 11.9 years), and 1 in the O group (73 years). In univariate analysis, diabetic foot was related to dialysis treatment (OR: 1.18, 95% CI: 1.09–1.29, $P = 0.02$), PAD (OR: 0.55, 95% CI: 0.47–0.64, $P = 0.01$)), VPT (OR: 12.6, 95% CI: 2.7–58.1, $P < 0.001$)), sensory loss (OR: 548, 95% CI: 52.9–56.82, $P < 0.001$)). Death was related to age (OR: 1.06, 95% CI: 1–1.11, $P = 0.02$)), dialysis treatment (OR: 1.17, 95% CI: 1.08–1.27, $P = 0.003$)), VPT (OR: 3.1, 95% CI: 0.99–9.8, $P = 0.04$)), loss of ankle reflexes (OR: 1.7, 95% CI: 1.1–2.8, $P = 0.007$)), and abnormal Neuropad response (OR: 1.1, 95% CI: 1.03–1.19, $P = 0.004$)). In multivariate analysis, only abnormal Neuropad test remained significant ($P < 0.05$; 26.4 ± 8.2 min in patients who had died and 17.8 ± 9.8 in alive; $P = 0.002$).
Conclusions
Sudomotor dysfunction is associated with increased mortality in patients with chronic kidney disease, with or without DM. Neuropad® test should be added as a sceening tool for diabetic foot syndroma. Both methods would be prognostic not only for the fate of leg but also fate of the patient.

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P450

Diabetic neuropathy in a young patient with recently diagnosed diabetes mellitus: an atypical presentation of insulin neuritis

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Introduction
Insulin neuritis is a rare form of presentation of diabetic neuropathy, usually associated with the sudden intensification of glucose control in individuals with long standing uncontrolled diabetes mellitus.
Objectives
To report a case of insulin neuritis in a young male, few weeks after diagnosis and insulin therapy initiation.
Clinical case
Male, 22 years old, previous history of excess weight until he was 19 years old, moment at which he began an intensive exercise regimen and lost 30 kg in the following 3 years. The general practitioner detected fasting hyperglycemia (404 mg/dl and 22.4 mmol/l) in routine analysis and he referenced the patient to urgent care of a diabetologist. He did not present with ketoacidosis, although he had ketonuria. He was positive for anti-GAD antibodies (31 IU/ml) and his C-peptide was 0.43 ng/ml. He initiated treatment with intensive insulin therapy in the endocrinology ward and was released with good glycemic control. Two months after discharge he presented with intense neuropathic burning-like pain, in both feet, and reduced leg muscle strength resulting in impairment of gait. Other causes of neuropathy were excluded. The electromyography was suggestive of diabetic neuropathy. Pain was controlled with pregabalin, tramadol, and amytriptiline, with clinical improvement. An overlooked previous episode of fasting hyperglycemia 3 years before was confirmed in the review of the clinical file of the patient.
Conclusion
Insulin neuritis is a variant of diabetic neuropathy that occurs with the fast resolution of hyperglycemia in patients with long standing unsatisfactory glucose control. This case occurred in a young individual with long-standing previously undiagnosed latent autoimmune diabetes, as suggested by the development of insulin neuritis. As such it is a rare presentation for this variant of diabetic neuropathy.

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Abstract withdrawn.

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Associations of serum lipid levels with diabetic retinopathy in type 1 diabetics

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Objective
Diabetic retinopathy was one of the important complications of diabetes both in type 1 or type 2 and cause blindness. High lipid levels was accused of endotheial dysfunction and so play a role in retinal exudate formation in retinopathy. The aim of this study was to acess the association between serum lipid levels and diabetic retinopathy.
Methods
Our study was carried out retrospectively in Istanbul Medeniyet University Goztepe Training and Research Hospital between 2012 and 2013. The cohort composed of 225 type 1 diabetic patients (114 males and 111 females) attending the diabetes outpatient clinic. Mean age was 38.23 ± 11.35 years (range: 17–80). LDL cholesterol, HDL cholesterol, TG, levels, anthropometric parameters, A1c, levels were obained from patients records. Statin user type 1 diabetics are excluded from the study. All of the patients were examined by same ophtalmologist. Patients diveded into two groups: patients without retinopathy and patients with retinopathy including non proliferative or proliferative retinopathy. Data analyzed by SPSS 17.0. Comparisons between different groups were performed by unpaired *t*-tests. Comparisons across categories were made using x^2. Correlations between variables of interest were performed by Pearson correlation.
Results
There were no difference according to gender and mean HbA1c levels in two groups ($P = 0.389$ and 0.245 respectively).The mean age of retinopathic patients are significantly higher than non rethinopathic patients ($P = 0.000$). There were no significant difference between normal group and retinopathic group acoordig to LDL and HDL cholesterol levels ($P = 0.268$ and 0.218 respectively). On the other hand there were significant difference between two groups on mean trigliserid levels ($P = 0.018$) group.
Conclusion
LDL and HDL cholesterol levels were not significantly associated with the presence of rethinopathy but trigliserides. Large multi-centric prospective studies are needed about this subject, especially to clarify the reasons of discrepancies between the findings of studies.

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Effect of diabetic nephropaty on lipid profiles of adult type 1 diabetics

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Objectives
Diabetic nephropathy is a common complication of diabetes. It can be a cause of abnormal lipoprotein metabolism and may be had an negative impact on metaboic control in diabetics. The aim of this study was to evaluate the effect of diabetic nephropathy on lipid profiles of adult type 1 diabetics.
Methods
Our study was carried out retrospectively in Istanbul Medeniyet University Goztepe Training and Research Hospital between 2012 and 2013. The cohort composed of 248 type 1 diabetic patients (128 males and 120 females) attending the diabetes outpatient clinic. Mean age was 37.4 ± 11.0 years (range: 17–74). LDL cholesterol, HDL cholesterol, TG, levels, anthropometric parameters, HbAlC, and urinary albumine levels were obained from patients records. Statin user type 1 diabetics are excluded from the study. Data analyzed by SPSS 17.0. Comparisons between different groups were performed by unpaired *t*-tests. Comparisons across categories were made using x^2. Correlations between variables of interest were performed by Pearson correlation.
Results
There were 39 (15.7%) patients with albuminurea. 37 patients was user of ACE blocker or ACE receptor blocers. There were no significant difference between normal group and nephropatic group acoordig to LDL cholesterol (111.40 ± 36.78 vs 121.00 ± 43.54 respectively $P = 0.148$). On the other hand there were also no significant difference between two groups neighter HDL cholesterol (56.62 ± 32.54 vs 51.61 ± 12.69 respectively $P = 0.345$) nor tiriglserid levels (106.44 ± 86.19 vs 127.94 ± 88.47) respectively $P = 0.156$). On the other hand in albuminuric group there were a positive corelation between LDL ($r = 0.679$, $P = 0.000$), triglyceride ($r = 0.685$, $P = 0.000$) levels and albumin levels in 24 h urine. This corelation is not valid for normoalbunuric group.
Conclusion
This study showed that LDL and HDL cholesterol, triglyceride levels do not show between albuminuric and normoalbunuric group but the levels of cholesterol show positive corelation in albumin levels in albuminuric group.

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P454

Vasoinhibins are natural inhibitors of angiogenesis in the vitreous and are impaired in patients with diabetic retinopathy

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With preterm regression of the hyaloid vascular system, the human vitreous becomes devoid of blood vessels and maintains an avascular, transparent state throughout life. However, diseases of the developing and mature retina, such as retinopathy of prematurity or proliferative diabetic retinopathy (PDR), often result in the invasion of blood vessels into the vitreous, with a risk of causing vitreous hemorrhage, retinal detachment and, consequently, loss of vision or blindness. Here, we investigated the role of vasoinhibins (Vi), antiangiogenic peptides derived from prolactin (PRL) by proteolytic cleavage, as natural inhibitors of angiogenesis in the vitreous. We demonstrate that incubation of PRL with human vitreous resulted in its cleavage to Vi in a time- and vitreous protein concentration-dependent manner. Further, we found that PRL cleavage was prevented by the matrix metalloproteinase (MMP) inhibitors galardin, phenanthroline, and EDTA. The vitreous from patients with PDR showed reduced PRL cleavage and higher proangiogenic effects in an endothelial cell proliferation assay relative to the control vitreous from non-diabetic patients. Control vitreous inhibited endothelial cell proliferation, and immunodepletion of Vi eliminated the anti-proliferative effect, indicating that Vi contribute substantially to the anti-angiogenic action. The presence of PRL in the vitreous was confirmed by an electrochemiluminescence immunoassay, and of Vi, and MMPs by western blotting. We conclude that Vi, generated by MMP-induced PRL cleavage, serve as vitreal inhibitors of angiogenesis and that their generation is impaired in patients with PDR.

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P455

The correlation of foetal ultrasound and HbA1c with birth weight in women with gestational diabetes

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Background
It is estimated that gestational diabetes (GDM) accounts for 87.5% of all diabetes cases in pregnancy and is associated with worse pregnancy outcomes. Macrosomia is one of the main complications of GDM and antenatal management strategies are directed at ensuring normal foetal growth. Ultrasonography is a useful tool for estimating foetal size, but there is little data in the literature correlating foetal abdominal circumference (AC) and birth weight in GDM. Furthermore, the use of HbA1c as a marker of glycaemic control (and hence pregnancy outcomes) in GDM is controversial. We therefore aimed to correlate AC measured at 36 weeks gestation and glycaemic control as measured by mean pregnancy HbA1c with foetal birth weight at delivery.
Methods
We performed a retrospective analysis of the biochemical results and ultrasound measurements of 496 women with singleton pregnancies who had had GDM diagnosed by OGTT at 26–28 weeks of gestation between 2008 and 2013. A statistical analysis was performed using the SPSS statistical package.
Results
The mean AC was 320 ± 24 mm (mean $\pm$ S.D.) and the mean foetal birth weight was 3208 ± 500 g (mean $\pm$ S.D.). There was a moderate positive correlation between AC and foetal birth weight (Pearson correlation coefficient 0.625; $P < 0.001$). There was no statistically significant correlation between AC or foetal body weight and the HbA1c test performed in the first/second and third month following OGTT (all $P > 0.10$).
Conclusions
Foetal ultrasound growth scan with measurement of the abdominal circumference is a useful tool in predicting foetal birth weight with positive correlation between foetal AC and birth weight endorsing current clinical practice. Although HbA1c is an established gold standard for assessing glycaemic control it provides little benefit in predicting macrosomia in the setting of GDM.

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P456

Undiagnosed diabetes mellitus presenting as thrombosis of the portal venous system: case report

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Introduction
Thrombosis of the portal venous system is rare with the prevalence about 1% in the general population reported previously, difficult to diagnose and can be fatal**.** We report a case of previously-undiagnosed type 2 diabetes mellitus presenting as portal venous system thrombosis and reviewed the pertinent medical literature.
Case presentation
A 54-year-old white female was admitted to our hospital with 10 days history of vague abdominal pain, nausea, vomiting and fever. Last months she had symptoms suggestive of diabetes mellitus. The degree of her subjective pain was disproportionate to her objective tenderness. Laboratory work-up revealed hyperglycemia, HbA1c 12.4%, a high total leukocyte count, lipase and amylase were normal, AST, ALT initially were normal. In the urine-analysis resulted urinary infection and positive ketone. An abdominal computed tomography (CT) with contrast had permitted the diagnosis of portal vein, splenic vein and superior mesenteric vein thrombosis associated with extensive hepatic, lineal, infarction and a tromb in descendent aort. Immediately, an anticoagulant therapy was conducted with intravenous heparin, but after 45 days treatment she died.
Results
In our case, the thrombus was secondary to a combination of comorbidities, including dehydration, urinary infection, ketosis and diabetes mellitus and the diagnoses was not made in time. Only a CT abdominal permitted the diagnosis of portal venous system thrombosis. Despite the anticoagulant therapy the result was fatal.

Conclusion
Thrombosis of the portal venous system is rare with the prevalence about 1% in the general population reported previously, difficult to diagnose and can be fatal. The clinical supposition of this diagnosis is based on the discrepancy between the abdominal pain and the physical examination. Abdominal CT is the test of choice for the diagnosis. A rapid diagnosis and an anticoagulant therapy administrated early are the most important factors for prognosis and survival rate.

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P457

Diabetic ketoacidosis and olanzapine: case report

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Introduction
Patients with psychotic or depressive disorders have an increased risk of developing metabolic syndrome, not only because of their unhealthy lifestyle (sedentary habits, inadequate diet and smoking) but also because of the negative impact of antipsychotic agents (specially clozapine and olanzapine) on several metabolic features. These include overweight/obesity, dyslipidemia, development of new-onset type 2 diabetes, worsening of pre-existing diabetes and diabetic ketoacidosis.
Case report
38-year-old man, with bipolar disorder, obesity (BMI 39 kg/m^2), dyslipidemia and a positive family history of type 2 diabetes. The patient had been taking quetiapine and lithium for the last years, with good tolerance. In 2013, due to an exacerbation of his psychiatric disorder, his psychiatrist prescribed olanzapine. Two weeks later, he developed polyuria, polydipsia and weight loss, which progressed to nausea and vomiting. He was admitted to our institution with the diagnosis of diabetic ketoacidosis, without any clinically evident precipitating event. Serum C-peptide level was 2.02 ng/ml and HbA1c 13.7%; islet cells and glutamic acid decarboxylase auto-antibodies were not measured. After stabilization, he was discharged, on metformin and a basal-bolus insulin regimen, and referenced to our Outpatient Clinic. When he was reevaluated, already without olanzapine, it was possible to decrease total daily dosage of insulin. Months later, insulin therapy was stopped and now he is on metformin 1500 mg/day and sitagliptin 50 mg/day, with a good metabolic control.
Discussion
The characteristics of the patient and his HbA1c suggests he had an undiagnosed type 2 diabetes, which manifested as a diabetic ketoacidosis. The temporal relationship between the introduction of olanzapine and the development of diabetic ketoacidosis suggests a causality relationship.
Conclusion
This case report illustrates one serious complication of the antipsychotic agents and stresses the importance of an evaluation of the metabolic risk and an individualized selection of the antipsychotic agent on these patients.

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P458

Intima: media thickness and endothelial dysfunction in GCK and HNF1A MODY patients

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Mutations in the (glucokinase) GCK gene are, along with the HNF1A gene mutations, the most frequent cause of (maturity onset diabetes of the young) MODY. Heterozygous loss-of-function GCK mutations result in a moderate fasting hyperglycemia. The GCK-MODY patients are usually free from microvascular complications; however, little is known about atherosclerosis and intermediate related phenotypes. We aimed to examine intima-media thickness (IMT) and endothelial function in GCK-MODY and HNF1A-MODY. 62 GCK-MODY, 40 HNF1A-MODY patients and 44 non-diabetic controls were examined. Carotic artery IMT and brachial artery FMD and (nitroglycerin mediated dilatation) NMD were assessed by ultrasonography. These parameters were compared with test for difference between two groups (*t*-test or Mann–Whitney *U*-test) or three groups (one-way-ANOVA or the Kruskal–Wallis test with *post hoc* test).
BMI was similar in all three groups – 23.8±4.4, 24.1±3.7 and 24.0±3.8 in GCK-MODY, HNF1A-MODY and controls respectively ($P=0.6930$). Patients were diagnosed with diabetes at similar age (GCK-MODY: 25.6±13.7 years vs HNF1A-MODY: 27.2±12, $P=0.6334$). Glycemic control was similar in diabetic groups as in the GCK-MODY group the mean HbA1c was 6.4%±0.7, while in HNF1A-MODY patients it reached 6.7±1.4 ($P=0.9274$). The average maximum IMT was not different – 0.71±0.17 mm in GCK-MODY, 0.75±0.14 in HNF1A-MODY, and 0.7±0.15 in the controls ($P=0.1251$). Mean IMT were as follow – 0.62±0.15 mm in GCK-MODY, 0.67±0.12 in HNF1A-MODY and 0.62±0.12 in controls ($P=0.0267$). *Post hoc* analysis showed a difference between GCK-MODY and HNF1A-MODY ($P=0.0427$). The mean FMD was 11.1±4.7% in GCK-MODY, 10.0±5.0 in HNF1A-MODY and 14.2±4.9 in the controls ($P=0.0031$). The differences between GCK-MODY and HNF1A-MODY vs controls were significant ($P=0.0043$, $P=0.0002$ respectively).
Both examined MODY groups showed evidence of early atherosclerosis or endothelial dysfunction. Mild hyperglycemia in the GCK-MODY seems to have impact on the occurrence of intermediate atherosclerotic phenotypes.

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P459

Prevalence of gastrointestinal diseases in the newly diagnosed pre-diabetic and diabetic patients

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Aim
Delayed gastric emptying affects a substantial proportion of patients with long-standing diabetes. On the other hand changes in gastric incretin hormones also play an important role in the pathophysiology of diabetes. In our study, we aimed to investigate the incidence of gastrointestinal disease in patients with newly diagnosed diabetes and pre-diabetes.
Methods
A total of 73 patients with newly diagnosed pre-diabetes and diabetes were included in the study. Patients were examined in detail, gastrointestinal disorders and gastrointestinal medications were recorded. Furthermore, during admission, a questionnaire for gastrointestinal disease; gastrointestinal symptoms rating scale (GSRS) was performed. Data were compared in patients with pre-diabetes and diabetes.
Results
Mean age of diabetic patients ($n=39$) was 47.6±8.7 while 39.8±14.6 of pre-diabetic patients ($n=34$) ($P=0.009$), and mean HbA1c levels were found 7.8±1.9 in patients with diabetes, 5.8±0.4 in patients with pre-diabetes ($P<0.001$). Fasting blood glucose (FBG), postprandial blood glucose (PBG) and creatinine levels were higher in patients with diabetes compared to pre-diabetes (FBG 156.7 and 99.4, PBG 230.7 and 143.2, creatinine 0.8 and 0.6). The average total GSRS scores were 5.95±3.9 and 4.59±4.2 in patients with diabetes and pre-diabetes respectively ($P=0.09$). The frequency of gastrointestinal diseases were 38.5% in diabetic patients and 11.8% in the pre-diabetics ($P=0.009$). Gastrointestinal drug use (GIDuse) were observed in 20.5% of diabetics and 5.9% of pre-diabetics ($P=0.060$). No correlation was detected with the presence of gastro-intestinal disease between age, biochemical parameters, HbA1c level or BMI.
Conclusion
In patients with long standing diabetes, gastroparesis, is a known complication. However, in our study, presence of gastrointestinal diseases was significantly higher in patients with newly diagnosed diabetes when compared with pre-diabetic patients. When also considering incretin hormone effect, contributing of gastrointestinal diseases to the development of diabetes maybe become obvious.

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P460

The influence of type 2 diabetes mellitus on periodontal disease

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The relationship between periodontitis and diabetes mellitus (DM) is widely accepted. Several studies identified a greater incidence of periodontitis and an increase of its severity in diabetic patients, approximately threefold.
In this study, we want to investigate the influence of type 2 DM (T2DM) in the development of periodontitis.
Single center, randomized trial with 90 patients T2DM. Exclusion criteria: chronic renal disease (GFR <90); pregnancy; antibiotics (last 3 months); hemoglobinopathies; bleeding disorders; less than three teeth; periodontal treatment (last 6 months) and smoking habits. Metabolic and biometric parameters were registered and used a computerized periodontal probe to record periodontal status. Variables were analyzed by χ^2 tests and multivariable regression with a significance level of 5%.
A total of 90 individuals were observed: 70 males (77.8%); mean age of 64.3 years ($\pm$9.95), BMI of 29.1 kg/m^2 ($\pm$4.42), waist circumference of 103.4 cm, HbA1c of 6.69% ($\pm$0.95), T2DM was diagnosed for 11.3 years ($\pm$8.66), and 84% had dyslipidemia. Patients had in average 21.4 teeth ($\pm$7.1), 98.1% of teeth had bleeding on probing, 11.1% had suppuration and 100% had dental plaque. CAL ranged from 0 to 11 mm. PD was present in 98% of T2DM patients: 55% had initial PD, 30% moderate and 15% severe.
There is an association between metabolic control (HbA1c) and the severity of PD ($P<0.001$) but not with the duration of T2DM ($P=0.415$). From multivariable analysis it was found that regardless metabolic control, diabetic patients had a higher risk of develop PD if they were obese or with higher waist measure ($P<0.001$) and dyslipidemia ($P=0.025$).
We conclude that patients with T2DM had a high prevalence of PD and similar to other diabetes complications, susceptibility to periodontitis is increased with poor glycemic control. Obesity, high waist circumference and dyslipidemia are a risk factor for PD even with a good glycemic control.

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P461

Diabetes and end-stage renal disease: clinical evaluation of diabetic renal transplant candidates

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Introduction
Diabetes mellitus (DM) is one of the main causes of end-stage renal disease (ESRD). Renal transplantation is the most effective form or renal replacement.
Methods
Retrospective, descriptive study of a sample of 108 diabetic patients admitted as candidates to renal transplant from January 1991 to December 2011, using the SPSS programme, version 20.0.
Results
11 women and 97 men were evaluated (medium age: 58$\pm$8.2 years (minimum: 34, maximum: 71). 86.1% had type 2 diabetes (T2DM), 10.2% had type 1 diabetes (T1DM) and 3.7% had other types of diabetes. The medium age of diagnosis ($n=104$) was similar in both sexes (women: 41.3$\pm$14.0 vs men: 42.2$\pm$9.1 years), but inferior in T1DM (32.8$\pm$12.0). The medium duration of the disease was 16.0$\pm$8.8 years, higher in T1DM (19.8$\pm$10.7 years). 69.4 % of patients were under insulin therapy. The medium A1C was 7.3$\pm$1.6%. 69.4% ($n=75$) of patients had retinopathy, and 17.3% of these had uni or bilateral amaurosis. 35.2% of the sample had neuropathy, 21.3% had peripheral vascular disease (PVD) and more than half of these (52.2%) were already submitted to amputation. 21 patients had ischemic heart disease (IHD) and 13 cerebrovascular disease (CBVD). Concurrently, 85.2% also had hypertension, 31.5 % had dyslipidemia, and 77.2 % of the patients where BMI was determined ($n=92$) were overweight or obese (medium BMI: 27.3 kg/m^2). After an average wait time of 1.31$\pm$2.4 years, 32 candidates were transplanted. These patients tended to be younger (medium age: 52.5$\pm$8.3 years vs 60.3$\pm$7.1 in the non-transplanted), mostly men (87.5%) and T2DM (78.1%). However, the percentage of transplanted women was superior to the percentage of men (36.4 vs 29.9%), and the percentage of T1DM was higher than T2DM (36.4 vs 26.9%). Transplanted patients had an inferior medium duration of diabetes (14.3$\pm$7.8 vs 16.7$\pm$9.1 years), and the percentage of microvascular complications in these patients was: retinopathy – 68.8%; amaurosis–3.1%; neuropathy – 18.8%; PVD – 12.5%; amputation – 6.25%. About 15.6% of transplanted patients had hypertension, 28.1% had dyslipidemia and 20 patients were overweight/obese.
Conclusions
The extent of micro and macrovascular complications of diabetes is determinant to the decision of renal transplantation in diabetic patients with ESRD.

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Diabetes therapy

P462

The role of the community pharmacist in managing patients with diabetes type 2

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Objective
Of this study is to evaluate if a pharmaceutical care program could improve glycaemic control in patients with diabetes.
Aim
The aims of the study are: i) to reinforce the lifestyle advice given to patients with diabetes at annual and other reviews. ii) to improve glycaemic control in patients with diabetes and improve patients adherence to medication. iii) to encourage participation to structured group education for diabetes patients.
Setting
This study was conducted in a community pharmacy in the city of Lezhe, in northwestern Albania.
Method
This project evaluates the pharmacist's interventions during a prospective randomized controlled trial, from September 2012 to May 2013. Patients with diagnose of diabetes mellitus type 2, regular customers of the pharmacy were allocated in a random way either to a control group or to an intervention group during a 9-month period). The pharmacist interventions, tried to increase medication adherence and glycaemic control in these patients, involved diabetes education sessions and counseling directed to the patient.
Results
A total of 120 diabetic patients were randomly assigned to the study (60 in the control group and 60 in the intervention group). Although there were no significant differences in both groups, at the end of the study, glycaemic control was higher in the intervention group ($P=0.005$). Medication adherence was also higher in the intervention group at the end of the study. There was also a decrease in the blood pressure in the intervention group.
Conclusion
Pharmacist intervention can significantly improve medication adherence and glycaemic control in patients with diabetes. Community pharmacists are valuable members of multidisciplinary health care teams in the management of patients with diabetes. Pharmacist interventions can improve medication adherence and reduce HbA1c values.

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P463

Trends of oral anti-diabetic drug usage amongst general practitioners of North-East India: an audit

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Objective
To study the usage of oral antidiabetic drug (OAD)s prescribed to T2DM patients by General Practitioners and to compare overall glycaemic status of different OAD users at the time of referral to a tertiary care clinic.
Methodology
T2DM patients attending a referral clinic underwent a proforma-based interview on their first visit. Data regarding subjects' ongoing prescription (at least for preceding 3 months with a compliance rate $\geq$80%) of OADs such as sulfonylurea, metformin, thiazolidinediones, α-glucosidase inhibitors, incretin, glinides as prescribed by General Practitioners were collected. HBA1c levels were estimated by HPLC (BIORAD). Results were expressed as mean$\pm$s.d.. HbA1c in two comparative groups were compared using two-tailed Student's *t*-test.
Results
Total 500 T2DM patients (male 61%, age 52.49$\pm$10.94 years, duration 7.31$\pm$6.16 years) were included in the study (attending clinic between November 2009 and February 2013). Only 24% of subjects were on monotherapy (using any one of the six OAD groups) at the time of referral. Average duration of diabetes in patients who were on monotherapy was 6.7$\pm$6.8 years whereas that of polytherapy was 7.5$\pm$5.9 years. The glycemic status as indicated by HbA1c level between these two groups has a highly significant difference (7.92$\pm$2.14 vs 8.79$\pm$2.16; $P=0.000142$). The most commonly used single OAD was sulfonylurea (52%) followed by metformin (34%). However, HbA1c level between these two groups did not differ much (7.85$\pm$1.84 vs 7.92$\pm$2.07; $P=0.80$). Sulfonylurea plus metformin (52%) was the most preferred combination of antidiabetic therapy. About 30% of patients were on triple drug therapy, the most commonly used combination being that of sulfonylurea plus metformin plus thiazolidinediones.
Conclusion
Sulfonyurea is the mostly preferred oral antidiabetic drug as monotherapy by the general practitioners of North-East India. Patients on polytherapy have a longer duration of diabetes and poorer control. This study indicates the current trend of diabetes practice prevailing in North Eastern part of India.

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P464

The outcome of β cell function after early insulin therapy in the recently diagosed type 2 diabetes (in Egyptian population) our experience in EL-Minia university hospital

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Background
Worsening hyperglycemia in type 2 diabetes may be due to continuous decline in insulin secretion secondary to β-cell dysfunction and decreased insulin sensitivity. The purpose of this prospective cohort study was to evaluate whether early insulin therapy is more advantageous in achieving long-term optimal glycemic control with improved B cell function than oral drugs in the recently diagnosed type 2 diabetes mellitus.
Methods
Sixty consecutive patients with recently diagnosed type 2 diabetes mellitus were divided into 3 groups. The 1st group received 2 SC injections of premixed insulin. The 2nd group received bed time NPH and 3 injections of regular insulin before meals. The 3rd group received metformin and/or sulphonylureas. The treatment continued for 3 months till euglycemia was reached. Then, all medications were stopped and the patients were followed up till the end of the year. BMI, FBG, PPG, HbA_{1C}, fasting level of insulin, proinsulin, C- peptide, HOMA-IR, HOMA-B, serum cholesterol, triglycerides were estimated.
Results
Six patients from group I (30%), nine from group II (45%), and only one from group III (5%) succeeded to maintain euglycemia without further therapy for 9 months after stoppage of treatment. The mean HbA_{1C} level was 6.5% in group I, 6.1% in group-2, and >7% in the group-3. Level of HbA_{1C} in the succeeded patients declined significantly in comparison to the failed patients. Markers of β-cell function of the succeeded patients showed a statistical significant increase regarding the C-peptide, insulin and HOMA-B. Meanwhile, proinsulin level and proinsulin/insulin ratio declined ($P=0.0001$). The total serum cholesterol and triglycerides of insulin treated groups reduced significantly ($P=0.001$).
Conclusions
Short-term insulin therapy in a newly diagnosed type 2 diabetes naive patients can preserve β-cell function and insulin secretion, allowing long-term glycemic control without medication and may improve glycemic responses to supplemental oral treatment if needed.
Keywords
Type 2 DM, early insulin therapy, B cell function
Abbreviations
BMI: Body mass index, FBG: fasting blood glucose, PPG: postprandial glucose, HbA_{1C}: Glycosylated haemoglobin, OADs: oral antidiabetic drugs, HOMA-B: homeostasis model assessment of ß-cell function, HOMA-IR: homeostasis model assessment of insulin resistance.

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P465

Metabolic control of our turkish diabetic patients on exenatide therapy: good at metabolic control but how about compliance?

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Objective
Our aim is to evaluate the effect of exenatide treatment on body weight, HbA1c and compliance to treatment.
Material and method
A total of 36 (five M and 31 F) type 2 diabetic patients who were prescribed exenatide were evaluated for this study. Body weight, BMI, HbA1c parameters and side effects were noted from the outpatient clinic records.
Result
The median age of our patients was 52 years of old (19–79 years). Median duration of diabetes was 9 years. Median duration of exenatide therapy was 9 months (1–23 months). While mean HbA1c value before exenatide was 8.7% (6–12.6%) and decreased to 7.5% (5.4–10.6%) with exenatide treatment. This decrement was significant ($P<0.05$ Table 1). Mean body weight before the treatment was 118 kg (81–197 kg). After treatment mean body weight decreased to 109 kg (72–175 kg) significantly ($P<0.05$ Table 1). Adverse events were observed in 25% of our patients ($n=9$). Acute pancreatitis was not seen in any of our patients. Treatment was discontinued in 33% of patients ($n=12$). The reasons of discontiuation were drug side effects in 42% ($n=5$), drug inefficacy in 16% ($n=2$) and remaining 42% ($n=5$) of the patients discontinued treatment without informing their physicians. However, two of those five patients had lost weight between 2–6 kg in first 2 months of their treatment.

Table 1 Changes in HbA1c, body weight and BMI, as mean$\pm$s.d.

	Before exenatide	After exenatide	*P* value
HbA1c (%)	8.7$\pm$1.6	7.5$\pm$1.3	0.001
Body weight (kg)	118.9$\pm$28.1	109.4$\pm$25.6	0.001
BMI (kg/m^2)	44.6$\pm$8.6	41.1$\pm$7.5	0.001

Conclusion
Exenatide treatment resulted in decrease in HbA1c and significant weight loss in our patients. Rate of side effects mainly nausea and vomiting was similar to the previous reports. But, it was observed that compliance to treatment was a little bit lower compared to good metabolic control of the treatment. To improve the compliance the health insurance policies should be reevaluated. As a suggestion for practitioners, those patients prescribed exenatide should be followed-up closely.

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P466

Effect of 7 weeks endurance exercise on insulin resistance and RBP4 protein expression in liver and adipose tissue in type 2 diabetic rats

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Introduction
Previous data shows that weight reduction decreases serum retinol binding protein-4 (RBP4) level. But it is not yet clear whether decreases in body weight resulted from exercise, will be accompanied by the changes of RBP4 protein expression in liver and adipose tissues in type 2 diabetes. Thus we designed this study to evaluate the ability of 7 weeks exercise to reverse the changes in body weight, insulin resistance (IR), serum RBP4 and its expression in liver and adipose tissue in high fat diet- STZ induced type 2 diabetic rats.
Method
Age matched male wistar rats were randomly divided to one of four groups: control (C), control trained (CT), diabetic untrained (DU) and diabetic trained (DT) ($n=6$ each group). A combination of high fat diet (HFD) and STZ injection were used to induce diabetes in DU and DT groups. Finally both CT and DT groups underwent a 7 weeks treadmill running at low speed. Rats were 18-week-old when tested. Serum RBP4 and tissue RBP4 protein expression were measured using Elisa and western blot respectively.
Results
Exercise causes a significant decrease in body weight in DT group. Moreover exercise leads to reduction in IR and serum concentration of RBP4. Although these values are significantly lower in DT group compared to DU group but still did not reach to the level of the C group. Exercise also significantly decreased RBP4 protein expression in liver and visceral fat tissue. However this reduction also didn't reach to the levels of the C group.
Conclusion
These findings suggest that despite completely normalizing body weight, exercise partially improved IR, serum RBP4 and its protein expression in liver and visceral fat in diabetic rat induced by HFD and STZ injection.

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P467

Diabetic ketoacidosis simulator: a new learning tool for a life threatening condition

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Introduction
Diabetic ketoacidosis (DKA) remains a life threatening complication in type 1 diabetes. Appropiate initial management is crucial in the evolution of this complex condition, and mistakes in the treatment are not uncommon.
Medical simulation technology is a powerful tool for training physicians but papers dealing with DKA simulators are scarce.
We introduce a new simulator designed in our institution aimed to junior doctors' training in DKA treatment whose implementation permits physicians to solve more case than what they would manage in the Emergency Room.
Material and methods
A software was developed by using mathematic algorithms based in previously published and empiric formulas to simulate the evolution of DKA both under appropriate and inappropriate management.
Results
The DKA simulator shows several cases to the trainee. Every case is compound by a clinical history and some variables which define the basal situation of the simulated patient: sex, age, weight, glucose, 3-β-OH-butyrate, sodium, potassium, serum creatinine, renal function, grade of dehydration, insulin sensitivity and ability to hyperventilation. The last four parameters are not shown to the trainee, but used by the simulator.
The trainee has to indicate the initial management, ask for biochemical test when necessary, and make successive changes in the treatment (iv insulin rate, type and rate of fluidotherapy and potassium administered) until DKA resolution is reached or, eventually, the death of the patient happens if the management has not been correct. By using mathematical algorithms, and according to the characteristics and the duration of the treatment, our simulator provides a clinical and biochemical evolution in the patient.
Conclusion
Our DKA simulator is a new tool whose objective is the training in a severe, frequent and complex situation, and can be used to improve the approach made by the junior physicians to the real diabetic patient.

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P468

Does statin use impairs glycaemic control in type 2 diabetic patients? A retrospective analysis

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While statins which are used safely to treat dyslipidemia, and improve cardiovascular mortality, recent articles claim that they also impairs glycaemic control in type 2 diabetes patients. Meta-analysis of larger scale studies indicate that use of statins is associated with an increase of 9% in diabetes onset. Despite that, we know not much about their effect on glucose regulation in patients already diagnosed with diabetes. Therefore, we aimed to investigate the effect of statins on glycaemic control in a sample of patients applied to an outpatient clinic. Because of the longer diabetes duration of the study population, co-morbidities like hypertension and dyslipidemia were almost always existing in subjects. So that it was difficult to establish a control group of subjects who do not use statins. This fact led to a small size control group in this study. The statin treated group enrolled 119 patients, while the non-statin group consisted of 28 patients. Patients were using statins in intervals to manage the targeted LDL level (<100 mg/dl). In 79.8% of patients, the targeted LDL level was maintained. The mean age of the study population was 66.8 ± 11.6 (31–93) years. Mean diabetes duration was 10.5 ± 8.9 (1–49) years. Male-to-female ratio was 0.67:1. All statistical comparisons were made by adjusting both groups according to age, diabetes duration, medication for diabetes (metformin, sulphonylurea, and insulin), anti-hypertensive medication including diuretics, β-blockers, ACE inhibitors, and ARBs. Mean HbA1c percentages in the statin and non-statin group were 7.0 ± 0.1 and 6.4 ± 0.2 S.E.M. respectively ($P=0.02$). Mean follow-up duration of the whole study population was 44.3 ± 35.4 (6–139) months with a median of 4 (2–7) HbA1c measurements *per se*. We conclude that besides increasing diabetes onset, statins also have a significantly negative affect on glucose control during routine follow up of diabetic patients.

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P469

Effect of angiotensin receptor blockers on glycaemic control in type 2 diabetic patients? A retrospective analysis

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Experimental and clinical studies suggest that blocking the effects of angiotensin II increases insulin sensitivity, skeletal muscle glucose transport, and pancreatic blood flow which may contribute to the prevention of diabetes mellitus. Although large scale studies and meta-analysis reveal that the new onset of diabetes could be significantly decreased by ARBs in both hypertensive and normotensive patients, their effect on glucose regulation in patients already diagnosed with diabetes has not been investigated in a satisfactory manner. The aim of this study is to evaluate the effect of ARBs on glucose regulation in a diabetic population. All subjects were randomly selected using their electronic records. Mean follow-up duration of the whole study population was 44.3 ± 35.4 (6–139) months with a median of 4 (2–7) HbA1c measurements *per se*. The mean age of the whole study population was 66.8 ± 11.6 (31–93) years. Mean diabetes duration was 10.5 ± 8.9 (1–49) years. Male-to-female ratio was 0.67:1. All statistical comparisons were made by adjusting both groups according to age, gender, diabetes duration, medication for diabetes (metformin, sulphonylurea, and insulin), smoking habits, β-blocker and diuretic use. Of the chosen study group 81.6% were using at least one anti-hypertensive medication. Among them 55.8% ($n=67$) were under ARB treatment with or without diuretics. When comparing subjects using ARB with subjects treated otherwise, we found that ARB treatment is related to significantly lower mean HbA1c levels ($P=0.013$). While the mean HbA1c level of ARB treated group was 6.6%, levels for non ARB treated group was found to be 7.1%. Although the population of this study group is not sufficient to make larger scale conclusions, we anticipate that patients with diabetes will benefit from ARBs in regard to glucose control.

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P470

Comparison of angiotensin receptor blockers and angiotensin converting enzyme inhibitors for glycaemic regulation

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Large scale clinical studies and meta-analysis suggest that treatment with angiotensin receptor blockers (ARBs) and angiotensin converting enzyme inhibitors (ACEIs) could have protective effect against diabetes development. While diuretics and β-blockers have some well known adverse effect on glycaemic regulation, ARBs/ACEIs' effect on glucose regulation in patients already diagnosed with diabetes has not been investigated well enough. Also to the best of our knowledge, direct comparison between ARBs and ACEIs for glycaemic control has not been investigated as well. The aim of this study is to compare the effect of ARBs and ACEIs on glucose regulation in a diabetic population. All subjects were randomly selected using their electronic records. While 37% ($n=39$) of the study population were using ACEIs, the remaining 63% ($n=67$) were using ARBs as monotherapy or in combination. Patients who are under monotherapy for hypertension with ARBs or ACEIs were found to be similar (20.5 and 19.4%, $P=0.89$). Mean follow-up duration of the whole study population was 44.3 ± 35.4 (6–139) months with a median of 4 (2–7) HbA1c measurements *per se*. The mean age of the whole study population was 66.8 ± 11.6 (31–93) years. Mean diabetes duration was 10.5 ± 8.9 (1–49) years. All statistical comparisons were made by adjusting both groups according to age, gender, diabetes duration, and medication for diabetes (metformin, sulphonylurea, and insulin), smoking habits, β-blocker, diuretic, and statin use. When comparing subjects using ARB with those on ACEIs, we found that ARB treatment is related to significantly lower mean HbA1c level (7.1 and 6.7%, $P=0.028$). Although the population of this study group is not sufficient to make larger scale conclusions, we anticipate that patients with diabetes will benefit more from ARBs rather than ACEIs in regard to glucose control. The reason may be related to the type of mechanisms of drugs action and degree of angiotensin II blockade.

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P471

Potential role of state of zinc metabolism in biguanides efficiency in hypoglycemic therapy

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It was proved that zinc complexes of both metformin and phenformin could act as protease inhibitors with potency at therapeutic concentrations. Biguanide-metal complexes turned out to be more potent cysteine protease inhibitors than either the biguanide or zinc ions alone, i.e. showed synergistic effect. It can be assumed that changes in state of metabolism of zinc induced by ageing, genetic predispositions, accompanying diseases, and some other drugs administered to diabetic patients affect the therapeutic efficiency of biguanides. Because with age serum concentration of zinc and level of its transmembrane transport are getting lower, a decrease of effectiveness of biguanides can be expected. The same effect is observed in a course of various acute and chronic diseases. In turn, some medications that induce an increase of serum zinc concentration and activate its transmembrane migration are probable to enhance a hypoglycemic efficiency of biguanides. The effects presented herein can be also discussed in relation to $Zn(2+)$-interactive inhibition of insulin degradation in hormone target tissues.

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Repetetive training of diabetic patient for medical nutrition and insulin therapy can improve the metabolic control

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Introduction
A successfull diabetes management is not only restricted to medical therapy but also includes a difficult and new life style adoptation. Errors frequently observed in patients such as not complying with their diet program, wrong way of doing insulin injections and insufficient insulin doses, hinder the adequate metabolic control of the disease. Also, physco-social status and different education levels complicate the effectiveness of the first training of the patient.
Aim
We aimed to investigate whether repetitive training of diabetic patients for medical nutrition and insulin therapy can improve the metabolic control of patients.
Method
Diabetic patients diagnosed according to the ADA criterias (19 type 1 DM; 108 type 2 DM; total: 127 patients) at Sisli Etfal Training and Research Hospital, Diabetes Mellitus Outpatient Clinics were enrolled in our prospective study. Patients were evaluated by demographic and antropometric parameters, medical history and their knowledge about diabetes and insulin therapy at first visit. Then, the patients were re-evaluated four times with an interval of 6 weeks by biochemically with fasting blood glucose and HbA1c, questioned for awareness and frequency of hypoglycemia, weight changes and the way of doing insulin injections. Training for diabetes and insulin therapy was repeated at each visit.
Results
Although over 84.3% of patients had been trained for diabetes, medical nutrition, and insulin therapy before the study, 51.4% of them were found to have a failure to comply with their diet and 60.6% had no habit of exercise. After repetetive training and frequent follow-up, HbA1c levels, and the frequency of hypoglycemia showed a significant gradual decline through the last visits ($P=0.0001$; $P=0.007$). Dosage of insulin administered per kilogram of weight was increased gradually through the last visit and mean weight of patients increased significantly ($P=0.005$; $P=0.002$).
Conclusion
Training for diabetes, medical nutrition and insulin therapy plays the most important role in the good metabolic control of diabetic patients. But physcosocial, economic and education levels of patients hinder the effectiveness of these trainings. As concluded in our study, questioning and repetative training of diabetic patient at each visit has a quiet effective role in the good metabolic control of diabetes mellitus.

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P473

Study on pregnancy outcomes in patients with type I diabetes mellitus having self-control skills

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The work was initiated to comparatively study pregnancy outcomes in patients with type I diabetes mellitus (DMI) with self-control skills and without them.
We examined 50 patients with DMI aged from 20 to 29 (mean age 24±3.2 years) ranging from those with newly diagnosed disease to those with DMI duration under 12 years. Glycemia and HBA1c levels were measured to assess carbohydrate metabolism.
40 patients with planned pregnancy having self-control skills were included into the first group, the second control one comprising ten patients referred for the specialized medical aid at various gestational ages. 3 months prior to pregnancy mean HbA1c level was 6.6±0.2 and 9.3±0.3% in the first and second groups respectively (normal range from 4.5 to 6.7%). All patients in the first group received intensive insulin therapy and completed self-control training under special program. In the second group not all women demonstrated patient compliance, most having unplanned pregnancy, but not completed special training. Mean fasting, postprandial, and average daily glycemia in the first group patients all through pregnancy was 6.0, 7.5, and 7.2 mmol/l respectively. In our study severe hypoglycemia absent, mild hypoglycemia episodes were compensated by the patients themselves ($n=18$, 36.6%). Mean fasting and post-prandial glycemia was 8.3±0.3 and 12.0 mmol/l respectively; HbA1c gradually reducing to 7.8±0.3% in the second group patients. Favorable outcomes of pregnancy were predetermined by sufficient compensation of carbohydrate metabolism. In the first group all 40 pregnancies completed with birth of viable children; thus, there were 24 natural deliveries and 16 cesarean sections for obstetrical indications. Fetopathy was registered in 13 (32.5%) newborns. In the second group eight pregnancies completed with birth of viable children, in one woman the pregnancy was terminated due to hydrocephaly at 19th week, in another one because of prenatal death. Eight newborns were born with fetopathy, one having macrosomia, and hypoglycemia. Planning of pregnancy in women completing self-control training with intensive insulin therapy regimen allows attaining adequate compensation of carbohydrate metabolism in patients with DMI and eventually results in favorable outcomes of pregnancy and deliveries.

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P474

Is psychological support the missing ingredient in successful outcomes for pancreas transplantation: the importance of recognising and managing the 'competitive patient'

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Introduction
To date, psychological research on pancreatic transplantation has focused mainly on illness and quality of life. Research has been predominantly quantitative rendering it impossible to identify specific psychological issues faced by patients. Uniquely, this work considered post-transplant issues in the context of the pre-transplant psychological burden of patients with T1DM.
Methods
21 individuals with T1DM were interviewed (11 males; five pre-transplant, 16 post-transplant). Time since transplantation varied from 7 weeks to 3 years. Individual semi-structured interviews were digitally recorded, transcribed verbatim and analysed independently by two researchers using inductive thematic analysis.
Results
'Diabetic identity' was a key theme. Failure to maintain good blood glucose levels despite participants' best efforts led many to 'give up' taking on a 'Failed patient' identity. Contact with some healthcare services reinforced the sense of failure. The shame associated with the need for help from third parties (e.g. family and work colleagues) to deal with the resultant hypos meant some participants 'felt like second class citizens'. Post-transplantation although they believed their identity to be 'still diabetic', some participants aspired to the identity of a successful transplant patient. This desire tended to manifest in competitive behaviour with possible adverse results on recovery, i.e. leaving hospital too soon, taking on too much at home, and returning to work too soon. These behaviours were associated with health-related problems.
Conclusions
Having a functioning pancreas, and being symptom-free, did not negate the experience and identity of having T1DM. Wanting to be rid of the sense of failure associated with having diabetes led some participants to make ill-advised decisions post transplant. If not recognised and managed appropriately, these behaviours could result in adverse health outcomes following transplantation, resulting in more frequent clinic attendance and delayed return to full activities of daily living, including delayed return to work.

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P475

Improvement of HbA1c is blunted following discontinuation of an on-line telemonitoring system, in patients with inefficiently controlled insulin-treated diabetes mellitus

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Aim
Primary goal was to determine whether the improvement of HbA1c, observed in inefficiently insulin-treated diabetes mellitus (DM) patients on a telemonitoring system, had a lasting effect following its discontinuation.
Methods
Forty-seven DM patients (mean age 56.15±15.86 years, mean BMI 29.44±6.69 kg/m^2, mean HbA1c 9.9±2.62%) and 25 insulin-treated matched controls (mean age 56.16±20.11 years, mean BMI 27.6±5.18 kg/m^2, mean HbA1c 9.92±2.45%) were enrolled. Patients' participation criteria included insufficient control of DM, distance from specialized medical facilities or recent hospitalization for DM. Data were transmitted from the glucose-meters to our computers via modem. Communication with the patients was achieved with e-mails and mobile-phone text messages through integrated software (Telemedicor). HbA1c and BMI were evaluated at enrollment, 3 and 6 months, as well as 6 months after discontinuation of the telemonitoring.
Results
A significant reduction in HbA1c was observed at 3 (6.93±0.88% in patients vs 8.04±0.87% in controls, $P<0.0001$) and 6 months (6.78±0.84% in patients vs 7.81±1.06% in controls, $P<0.0001$). Compared to controls, significant reduction was also observed in the group of patients with an initial HbA1c>10% (3 months: 6.83±1.06 vs 8.45±0.87%, and 6 months: 6.7±1 vs 8.17±1.21%) and HbA1c<10% (3 months: 7.02±0.67 vs 7.72±0.75%, and 6 months: 6.86±0.65 vs 7.52±0.86%). No statistical differences in BMI were observed between patients and controls.
Six months after discontinuation of the telemonitoring, patients' HbA1c levels deteriorated (7.25±1.02 $P<0.0001$). Significant increase was observed in both groups of patients with HbA1c>10% (7.35±1.35 $P=0.001$) and HbA1c<10% (7.17±0.62, $P=0.006$).
Conclusions
Telemonitoring DM patients can result in improved compliance especially in patients with HbA1c>10%. This is reflected in the reduction of HbA1c levels compared to the controls. Visits of outpatient departments are reduced, resulting in lower cost and less patient inconvenience. This beneficial effect is blunted 6 months after terminating the intervention.

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P476

Could favorable effects of liraglutide on steato-hepatitis be independent of weight loss in type 2 diabetes? A case report

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Introduction
Some data suggest a favorable effect of glucagon-like peptide 1 (GLP1) on steato-hepatitis (SH) in type 2 diabetes. We report here a case of improvement of SH in a patient treated by liraglutide.

Patients and methods
A 31-year-old woman presented type 2 diabetes. Her weight was 80 kg for 1.58 m (BMI = 32 kg/m^2). A treatment by liraglutide was initiated at 1.2 mg/day, percutaneously. A regular follow-up was performed with the recording of weight, HbA1c, iron and lipid status. Liver function was assessed regularly by liver enzymes dosage and fibromax score establishment.
Results
Before liraglutide initiation HbA1c was 8.6%, ASAT 45 UI/l, ALAT 58 UI/l, and GGT 174 UI/l. After only 3 months HbA1c dropped to 6.5%, ASAT 42, ALAT 52, and GGT 92 UI/l, as the weight was still 79.4 kg. At 1 year the results were: HbA1c 6.7%, ASAT 17 UI/l, ALAT 18 UI/l and GGT 26 UI/l. Triglycerides level decreased from 2.63 to 0.8 mmol/l. The FIBROMAX score indicated initially an important SH, which greatly improved at one year (Steatotest = 1 vs 3, Nashtest = 1 vs 2, and Actitest = 0 vs 1–2), while her weight was 74 kg.
Discussion
This observation suggests a beneficial role of liraglutide on SH in this patient. Proving that this could be independent of weight loss is difficult, as the patient had lost 6 kg in 1 year. However at 3 months Nash-test decreased to 1 as her weight remained stable. A beneficial effect of GLP1 analogs on SH independently of weight loss has been suggested in mouse. This effect could be due to an action of the GLP1 analog on hepatocytes, which usually express GLP-1 receptors, leading to fat export and increase of β oxidation. A prospective study including more patients is currently in process in our department, in order to assess this hypothesis.

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P477

Embryonal antitumor modulator's preventive action on streptozotocin induced damage of mouse pancreatic β cells in primary culture

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Introduction
β cells are a major target of therapeutic strategies to treat diabetes and are extensively studied in terms of their differentiation, function, and maintenance. β cell mass dynamically changes in response to altered metabolic demands in an organism. Many therapies are suggested including transplantation of pancreas or islet cells for type 1 diabetes patients, however these procedures are associated with significant risks and costs. Hence, search for new therapeutic modalities is extremely actual.
Design
Stretozotocin was used as diabetogenic agent. As an antidiabetic compound was used Embryonal antitumor modulator, created by Prof. L. Mkrtchyan (EATM-LM). Preparation of primary mouse β cell culture was conducted as described by Skelin *et al.* (2010). Pancreatic islet and β cell identity was confirmed by morphological studies of cell suspension and fixed cells stained with AzurII-eozin and immunostained with anti-insulin antibodies using light and fluorescent microscopy. Cells were counted in the Neubauer counting chamber with 600× magnification) and the results expressed by means of β cells count $\times 10^5$/ml. Tripan blue (TB) exclusion method was used to evaluate the effect of tested agents on cells viability. Agarose gel electrophoresis was used to assay of DNA damage value and character.
Results
EATM revealed pronounced protective activity in stretozotocin–induced damage of pancreatic β cells. In a primary culture of mouse pancreatic β cells EATM prevented stretozotocin action in different concentrations (0.01–0.1 mg/ml). EATM promoted survival of β cells damaged by stretozotocin. Moreover, EATM prevented the decrease of insulin production and DNA destruction in stretozotocin-damaged β cells.
Conclusions
The data obtained support the idea of the the appropriateness of EATM in diabetes therapy.

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Hypogonadal men with cardiovascular diseases benefit from long-term treatment with testosterone undecanoate: observational data from a registry study

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Background
Hypogonadism is associated with cardiometabolic risk. Studies suggest that hypogonadism increases the risk of all-cause and cardiovascular mortality. While some short-term studies have been performed in men with CVD, there are no data on long-term effects of testosterone replacement therapy (TRT) in men with CVD.
Methods
In a prospective, cumulative, observational registry study from a single urologist's office, 300 men with testosterone $\leq$12.1 nmol/l received TU injections for upto 6 years. In this subgroup analysis, 68 men with a previous diagnosis of coronary artery disease (CAD; $n = 40$) and/or a history of myocardial infarction (MI; $n = 40$) were analyzed.
Results
Mean age was 60.76 ± 4.94 years. 68 men were included for 2 years, 59 for 3 years, 54 for 4 years, 44 for 5 years, and 28 for 6 years. Declining numbers reflect the nature of the registry but not drop-out rates.
Weight (kg) decreased from 115.07 ± 13.71 to 92.5 ± 9.64. Waist circumference (cm) decreased from 112.07 ± 7.97 to 99.89 ± 6.86. BMI decreased from 37.27 ± 4.45 to 30.14 ± 3.21 ($P < 0.0001$ for all). Mean weight loss was 17.05 ± 0.57%. Fasting glucose decreased from 108.74 ± 17.08 to 96.0 ± 1.92 mg/dl, HbA1c from 7.81 ± 1.17 to 6.2 ± 0.62% ($P < 0.0001$ for both). Total cholesterol decreased from 304.66 ± 34.09 to 189.32 ± 9.68, LDL from 184.28 ± 37.51 to 134 ± 27.91, triglycerides from 308.38 ± 56.3 to 187.71 ± 8.67 mg/dl ($P < 0.0001$ for all). HDL increased slightly. The total cholesterol:HDL ratio declined from 5.16 ± 1.55 to 3.15 ± 0.87 ($P < 0.0001$). Systolic BP decreased from 167.82 ± 11.01 to 142.36 ± 10.62, diastolic BP from 102.28 ± 8.23 to 81.25 ± 8.07 mmHg ($P < 0.0001$ for both). Pulse pressure declined from 65.54 ± 5.24 to 61.11 ± 4.66 ($P < 0.0001$).
The minimum number of injections was 9, maximum 26. In no patient TRT was discontinued or interrupted. There were no major cardiovascular events during the observation time.
Conclusion
TRT in hypogonadal men with CVD was well tolerated and resulted in significant and sustained improvements of cardiometabolic risk factors. Adherence to TRT was excellent.

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Gastric contractility modulation: a novel method for the treatment of type 2 diabetes mellitus with overweight and obesity: a preliminary results of the clinical study

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Introduction
We present preliminary results of the treatment with DIAMOND system – novel method of therapy of type 2 diabetes (T2DM) associated with obesity, based on new technology – gastric contractility modulation (GCM).
Material and methods
In 23 overweight/obese patients with T2DM enrolled into the polish arm of the multicenter, prospective, randomized study device modulating gastric contractility was implanted. We present data from nine women and three men aged 41–61

years with BMI 28.1–42.5 kg/m^2 who completed to date third period of the study. DIAMOND™ system recognize natural electrical activity of the stomach and automatically apply nonexcitatory electrical stimulation treatment during eating with subsequent modulation of signals transmitted by vagus nerve to the regulatory centers in the brain in order to provoke en early response of the gut typical of a full meal. HbA1c, body weight, BMI and waist circumference were observed during the next 72 weeks.

Results

Results of the treatment turned out to be triglyceride-dependent. In group with initially low triglycerides significant decrease in HbA1c, body weight and waist circumference were observed: from 8.28±0.8 to 7.05±0.4, $P<0.04$; from 88.35±6.14 to 84.3±6.6, $P<0.04$; and from 111.4±4.8 to 103.7±7.8, $P<0.03$ respectively. In patients with high triglycerides results were not significant.

Conclusions

DIAMOND™ system is safe, well tolerated, and has significant impact on HbA1c and weight loss. This novel method of treatment addressed for type 2 diabetes patients with overweight/obesity may probably become an alternative to the use of the incretins or insulin. It may also substitute the bariatric surgery in obese patients who are unwilling to undergo vast and anatomically irreversible operation or do not meet all required criteria to justify these procedures. The DIAMOND™ system provide good glycemic control with minimal patient compliance and with a potential added benefit of body weight loss, but without GLP1 mimetics treatment related adverse effects.

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P480

The role of continuous subcutaneous insulin infusion therapy in a case of Seip–Berardinelli congenital lipodystrophy

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Introduction

Seip–Berardinelli congenital lipodystrophy (SBCL) is an extremely rare autosomal recessive disorder characterized by a congenital absence of adipose tissue. Hepatic steatosis, splenomegaly, skeletal muscle hypertrophy, hypertrophic cardiomyopathy, insulin-resistance and diabetes mellitus (DM) are some of the features of these patients.

Case report

A 20-year-old caucasian-male patient was referred to pediatric endocrinology unit at 6-month-age because of liver function alterations. On examination, muscular appearance with minimal subcutaneous fat and hepatosplenomegaly were identified. Laboratorial tests revealed abnormalities in cytolytic and cholestatic liver enzymes; glycemia was normal. Ultrasound exams documented diffuse liver steatosis and hypertrophic cardiomyopathy. The identification of heterozygous *BSCL2* gene mutation (p.Pro65ArgfsX28 and p.Thr109AsnfsX5) established the diagnosis of SBCL type 2.

At 7-year-old DM was diagnosed (fasting plasma glucose=182 mg/dl; HbA1C=8.8%; insulin=116.7 mU/l; C-peptide=8.7 ng/ml; and HOMA-IR=52.4). The patient was initially treated with metformin and later at 11-year-old with concomitant insulin. He had always a poor metabolic control, justifying at 16-year-old age (HbA1c=11.5%), the start on continuous subcutaneous insulin infusion (CSII) therapy. A significant improvement was obtained (last evaluation of HbA1c=8.0%). He is currently under metformin (4 g/day) and CSII therapy (daily dose of insulin of 155U).

Conclusion

We report a rare case of lipoatrophic DM in childhood associated with severe insulin-resistance within the context of SBCL. In this setting, DM is frequently difficult to control and the management may involve insulin-sensitizers and exogenous insulin. Although the CSII therapy is normally used in insulin-deficient patients, classically type 1 DM, some insulin-resistant DM patients, as the one reported, may benefit from this therapeutical approach.

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P481

Type 2 diabetic patients can benefit by switching from premixed insulin analogues to detemir and aspart insulin

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Introduction

Type 2 diabetes represents an important health problem and is designated by a progressive course, and the subsequent long-term insulin therapy to achieve optimal glucose control. It is important to stress that a substantial number of patients do not achieve optimal glucose control despite the usage of two doses of premixed insulin. Detemir insulin, along with a low pharmacodynamic coefficient of variability, exhibits anorexigenic features, through its effects on the CNS. The aim of the study was to determine the reduction in HbA1c and weight reduction in type 2 diabetic patients switched from premixed insulin analogues to aspart and detemir insulin.

Patients and methods

57 uncontrolled diabetic patients (26 males, 31 females, mean age 65.5±7.0 years, and diabetes duration 16.8±6.0 years) were enrolled and followed for 1 year. At the study entry patients were treated with premixed insulin analogues and switched to three doses of aspart preprandial, and one dose of detemir bedtime.

Results

26.3% of subjects achieved HbA1c $<$ 7%. A difference was observed in mean fasting plasma glucose (12.3±2.8 vs 9.3±2.4 mmol/l, $P<0.001$)) and mean HbA1c (8.48±0.83 vs 7.7±0.83%, $P=0.0002$). Body weight reduction of 3.45±1.81 kg was observed in the group of 22 patients with the highest BMI (32.54±3.24 kg/m^2). In 14 patients (BMI 31.07±2.91 kg/m^2) no change in body weight was found. Group of 21 patients with the lowest BMI (29.11±2.65 kg/m^2) gained 2.5±1.1 kg.

Conclusion

Intensification of insulin therapy with aspart and detemir resulted in significant improvement of glycaemic control, as well as in the reduction of body weight in 38.6% of patients. Exhibition of anorexigenic features of detemir with effect on body weight could be explained by the difference in dopaminergic activity.

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P482

Prospective study of healthy lifestyle on diabetes mellitus

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Diet and physical activity are éssensiels in support of diabetes mellitus (DM) as well as medical treatment.

Aim

Evaluate the results of diet and physical activity on anthropometric and metabolic parameters of T2DM patients untreated population and methodology. 30 newly diagnosed T2DM patients (20W and 10 M; mean age 56.23±0.96 years were placed under hygienodietetic rules. Each patient underwent a clinical examination specifying TT, BMI, and metabolic parameters (fasting glucose, HbA1c, HDLc, LDLc, TG, and CT) at the first consultation and 3 months after resultsBMI, TT and metabolic parameters means with the exception of HDLc in men decreased significantly after hygienodietetic rules. BMI: M before 27.81±0.52 (23.73–31.46) and after 26.22±0.51 (23.03–31.46) (P: 0.011). W before 32.48±0.68 and after 32.16±0.66 (P: 0.030). TT: M before 101.30±1.04 and after 99.20±1.13 (P: 0.007). W before 103±1.30 and after 100, 3±1.33 (P: 0,005). FPG: before 1.61±0.05 and after 1.24±0.034 (P: 0.000006). HbA1c: before 7.04±0.05 and after 6.33±0.061 (P: 0.0000001). Triglycerides: before 1.57±0.09 and after 1.25±0.04 (0.62–3.06) (P: 0.01). Cholesterol: before 1.90±0.03 (0.9–2.7) and after 1.59±0.02 (P: 0,0005). LDLc: before 1.23±0.03 and after 1.11±0.02 (P: 0.00003). HDL: M before 0.41±0.01 and after 0.42±0.01 (P: 0.64). W before 0.46±0.01 and after 0.47±0.01 (P: 0.09)

Discussion and conclusion

The rules of dietary and lifestyle remain the first step in the management of T2DM They provide satisfactory results justifying their recommendation

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Self-monitoring of blood glucose and perceived obstacles in Turkish patients with diabetes mellitus

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Aims
Self-monitoring of blood glucose (SMBG) is a necessary component of diabetes management but many patients with diabetes do not follow their healthcare proffesionals' recommendations for self-monitoring. The aims of this study were to determine the proportion of patients with diabetes who perform SMBG in general practice and to identify patient-reported obstacles for SMBG.
Methods
The study included 372 patients with type 1 or type 2 diabetes mellitus (DM), who attended to outpatient clinics of three State Hospitals. The patients were asked to report their SMBG frequency and if SMBG frequency was less than 4 tests/week, also asked what makes it difficult for them to check their blood sugars. Sex, age, years of education, diabetes duration, current medications for diabetes, HbA1c levels of the patients were also recorded.
Results
Among 372 patients, 337 (91%) reported having used SMBG during the past 12 months. Overall, 58.2% ($n=196$) of patients who self-monitored their blood glucose did one to three tests/week and 41.8% ($n=141$) of patients did ≥ 4 tests/week. The groups were similar by means of age, sex and years of education. Patients using insulin or insulin plus oral medication were more likely to report SMBG than were those using only oral medication (49.5 vs 30.1%; $P=0.000$). Mean HbA1c levels in less frequently testing group was significantly higher than more frequently testing group (9.4 ± 2.5 vs 8.8 ± 2.2%; $P=0,028$). The most frequently reported barriers for testing were; I do not see any value in checking more often (8.9%); I find it uncessary to check if I do not have any symptom (10.1%) and the results make me feel bad and I'd rather not check (8.6%).
Discussion
SMBG should be considered as an important tool for managing diabetes and addressing patients' self monitoring-related concerns and motivations may be usefull in reinforcing engagement with SMBG.

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Normal and extended release form of metformin in type 2 diabetıc and pre-diabetic patients.

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Aim
Metformin is usually well-tolerated and commonly used oral-antidiabetic in type-2 diabetes and pre-diabetes. The most common side effects are gastrointestinal (GI) ones. It is proposed that, extended-release form of metformin has less gastrointestinal side effects. We aimed to compare the extended-release and normal-release form metformin in type-2 diabetic and prediabetic patients for gastrointestinal tolerability, weight effect and glycemic control.
Methods
Seventy-three newly diagnosed type-2 diabetic or prediabetic patients (mean age 43.9 ± 12.1) enrolled in the study. Normal-release(group I, $n=39$) and extended-release(group II, $n=34$) metformin were started to patients with randomisation. Gastrointestinal symptom rating scale was used at the beginning and in the first month of treatment for evaluation. Weight effect of metformin forms and glycemic parameters (HbA1c) also considered.
Results
The number of patients diagnosed with diabetes were 39 (mean age 47.5 ± 8.7) and with prediabetes were 34 (mean age 39.8 ± 14.1), respectively. GI disease history were present in 26% of all patients with GI drug use in 13.7%. GI disease history or drug use did not differ significantly between the groups.Gastrointestinal symptom scores were similar in both groups at the beginning. At least one new symptom were found 20.5% of group I and 26.4% of group II. There was a slight increase in symptoms associated diarrhea in both groups and indigestion in the group II. No patients discontined treatment due to side effects. Weight loss was observed 3.31 and 3.44 kg for prediabetics, 2.38 and 2.75 kg for diabetic patients in the group I and II. In diabetic patients, HbA1c reduced 1.28% and 1.24% in the group I and II.
In conclusion, both forms are effective, well tolerated and similar in terms of gastrointestinal side effects.

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Teaching system of self-control in endocrinology

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The Republic of Belarus gained 20 years of experience in teaching patients self-control of diabetes mellitus and hypothyroidism.
Learning technique consists of work in small groups (5 to 6 people). Patients with newly diagnosed disease are subjects to training (one step). Then weekly at outpatient clinics they attend classes on specific subjects (duration of class is 1 hr). Each class consists of a short lecture, analysis of clinical cases, a class discussion of the results. Subjects of classes are regulated and approved by the Ministry of Health. Today at the Republic of Belarus function 237 schools of diabetes and 18 hypothyroidism schools.
Learning outcomes lead to better control of diabetes at home during long-term observation of HbA1c levels. During the first 2 years the amount of severe ketoacidosis halved and the incidence of hypoglycemia is three times lower. During 10 years period in patients, who perform self-control, the number of amputations because of diabetic foot syndrome decreased by 15%.
However, introduction of self-control teaching system in endocrinology has its problems.

i) Doctors and physician assistants not always have sufficient teaching skills which reduces the patient' motivation to perform self-control.
ii) Among medical personal there is a lack of interest in patient' self-control diary. Because of that at the Department of Endocrinology is conducted special training of teachers in order to prepare them for schools of diabetes.
iii) Training of patients with hypothyroidism is more difficult not only for teacher but for the patients themselves. These issues are currently relevant for endocrinologist that are connected with teaching process of such patients and are the subject of discussion at the meetings of the Republican Association of Endocrinologists. Teaching guidelines of self-control in hypothyroidism are being prepared to be issued.

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Treatment with dipeptidyl peptidase-4 inhibitors may induce bullous pemphigoid in patients with type 2 diabetes

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Aim
Recent reports of adverse skin reactions in patients receiving dipeptidyl peptidase-4 (DPP-4) inhibitors have increased awareness towards skin-targeting side effects. Bullous pemphigoid (BP) is an autoimmune blistering dermatosis with significant morbidity and mortality. We report the development of BP in patients with type 2 diabetes mellitus (T2DM) treated with DPP-4 inhibitors.
Method
Evaluation of the temporal distribution of the frequency of BP diagnoses with respect to T2DM comorbidity and the use of DPP-4 inhibitors during a 7-year-period (01/2007–12/2013) in a single center. The diagnosis of BP was based on clinicopathological correlation and direct and indirect immunofluorescent staining.
Results
Seventy consecutive patients with newly diagnosed BP were included in the study (age range: 64–95). At the time of BP diagnosis, 29 patients (41%) were co-morbid for T2DM, 20 of them (69%) under treatment with DPP4-inhibitors for 2–18 months (median 8) prior to BP diagnosis. Moreover, the number of patients with diagnosis of BP co-morbid for T2DM was unequally distributed in time, in correlation to the increasing use of DPP-4 inhibitors for T2DM following their introduction in 2007 in Greece ($P=0.03$, Fisher's exact test, comparison of frequency of T2DM in BP cases between 2007–2009 and 2010–2013 time periods). In particular, between 2007 and 2009 (when DPP4 inhibitor use in Greece was <6.3%) none of the BP patients with T2DM were on treatment with

DPP-4 inhibitors (4/22, 18%). However, between 2010 and 2013 (when DPP4 inhibitor use had increased to 9.4–15.7%), 29/48 (60%) patients with BP had T2DM and the majority of them (20/29 = 69%) were on DPP-4 inhibitors.
Conclusion
We report an increasing frequency of BP in T2DM patients on treatment with DPP-4 inhibitors, compatible with a group-specific adverse drug reaction. BP should be suspected in T2DM patients on DPP-4 inhibitors, especially elderly ones, who complain for the development of any itching dermatosis.

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Changes in insulin sensitivity and DHEAS in type 2 diabetic men treated with liraglutide

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DHEAS, an adrenal steroid which displays antiatherogenic and cardioprotective actions, has been pointed as a marker of insulin sensivity (IS). No studies have inquired the effects of liraglutide on DHEAS levels and its relatioship with IS in patients with type 2 diabetes.
Methods
We have studied 12 diabetic male patients (aged 48.6 ± 10.4 years), before and after 6 months of liraglutide therapy. Liraglutide was initiated at 0.6 mg/day for a week and 1.2 mg/day thereafter. We measured biochemical parametres and adrenal steroids. IS was assesed by HOMA-IR and β cell function by HOMA-β.
Results
There were a significant decrease in weight (114.6 vs 106.6 kg, $P < 0.001$), BMI (40.16 vs 35.06 kg/m^2, $P < 0.001$), waist perimeter (125 vs 120.3 cm, $P < 0.001$), HbA1c (8.05 vs 7.08%, $P < 0.001$), glucose (158.9 vs 126.2 mg/dl, $P = 0.010$), HDL (40.45 vs 42.54 mg/dl, $P = 0.013$), triglycerides (190.1 vs 151.5, $P = 0.010$) and HOMA-IR (6.13 vs 3.21, $P = 0.026$). Borderline signification was observed in DHEAS (237.1 vs 218.6 μg/dl, $P = 0.063$). There were no differences in HOMA-β, insulin, C-peptide, total cholesterol, LDL, cortisol, ACTH, androstendione, testosterone or SHBG. No correlation has been found between DHEAS and IS.
Discussion
The preliminary results of this ongoing study show that 6 months' therapy with liraglutide significantly improves metabolic control in patients with type 2 diabetes. Changes of borderline signification in DHEAS were also found with this treatment.

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Basal bolus insulin therapy in hospitalised patients with diabetes mellitus type 2 using two algorithms embedded in a tablet PC

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Current guidelines recommend pre-meal blood glucose (BG) levels of < 140 mg/dl in the hospital. The aim of this analysis was to compare two versions of a workflow-integrated algorithm for basal-bolus insulin therapy (REACTION algorithm) for glycemic management in patients with diabetes mellitus type 2 (T2D) hospitalized at the general ward.

For both algorithms BG measurements were performed four times daily (pre-breakfast, pre-lunch, pre-dinner, and at bedtime); insulin injections were given according to the algorithm advice algorithm. A basal-bolus regimen with advice for total daily dose (TDD) (50% basal insulin, 50% pre-meal bolus insulin with additional corrective dose if necessary) was generated once daily. In the refined algorithm bolus insulin dose was redistributed over the day whereas total daily dose and the 50:50 ratio remained unchanged.
Each algorithm was applied in 15 T2D patients (initial algorithm: four females, age 69 ± 10 years, HbA1c 76 ± 30 mmol/mol, BMI 29 ± 6 kg/m^2; refined algorithm: seven females, age 73 ± 11 years, HbA1c 62 ± 18 mmol/mol, and BMI 30 ± 7 kg/m^2). Mean BG was 163 ± 34 mg/dl (initial algorithm) vs. 148 ± 25 mg/dl (refined algorithm). 6/456 (1.3%) and 7/457 (1.5%) measurements were in the hypoglycaemic range (< 70 mg/dl), initial and refined algorithm respectively. In both groups no value was below 40 mg/dl. Mean TDD was 47 ± 28 U (basal: 20 ± 13 U and bolus: 27 ± 16 U) for the initial algorithm and 47 ± 27 U (basal: 22 ± 12 U and bolus: 25 ± 15 U) for the refined algorithm. Adherence to the insulin advices by the algorithm was 113/115 (98.3%) and 110/111 (99.1%) for TDD, 104/106 (98.1%) and 101/107 (94.4%) for basal insulin and 374/393 (95.2%) and 269/279 (96.4%) for bolus insulin (initial and refined algorithm respectively).
The refined version of the Reaction algorithm could improve glycaemic control without increased risk of hypoglycaemia. Adherence to insulin dosing advices generated by both algorithms was high. Insulin doses were comparable for the two versions of the algorithm. The reaction algorithm has the potential to improve glycaemic management in the hospital setting.

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Influence of different modes insulin on carbohydrate metabolism, state transplant, control of metabolic and hemodynamic factors in patients with type 1 diabetes during the 1st year after kidney transplantation

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Objective
To evaluate the impact of different modes of insulin therapy (continuous subcutaneous insulin infusion (CSII) using insulin pump or multiple insulin injections (MII)) on carbohydrate metabolism, the state of the transplant, cardiovascular system, calcium and phosphorus metabolism in patients with type 1 diabetes (DM1) during the 1st year after kidney transplantation (KT).
Materials and methods
The study included patients with DM1 after transplantation i) five patients treated with CSII and ii) five on MII. Mean duration of diabetes in the first group was 24 years (20; 25), the second group – 23 years (21; 23). Posttransplantation period in both groups was comparable 8 months (7; 8).
Results
The mean level of HbA1c in groups before the study did not different: 9.0% (8.0; 9.6) vs 9.3% (9.2; 9.8). When patients were transfer into CSII–HbA1c after 3-6 months was significantly lower in this group –7.5% (7.5; 7.8), while in the group on MII remained the same-9% (7.6; 9.1). In the group with MII continuing-poor glycemic control in one patient (20%) in the control terms diagnosed recurrent diabetic nephropathy at the stage of microalbuminuria-the level of albuminuria was 35 mg/l, reanalysis – 68.0 mg/l. All patients, treated CSII had normal albuminuria. GFR (EPI) in both groups was comparable: 67 ml/min per 1.73 m^2 (65; 86) and 65 ml/min per 1.73 m^2 (63; 109) respectively. Diabetic retinopathy mainly proliferative stage after repeated laser panretinal photocoagulation all patients stabilized. Positive dynamics of hemoglobin, parathyroid hormone, calcium phosphorus product, blood pressure did not differ between groups of patients after KT.
Conclusions
The CSII of using insulin pump allows faster and more efficiently reach target values glycemia in patients with DM1 after transplantation, which may improve the control of complications and overall prognosis.

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The effects of metformin therapy on bone resorption and bone formation markers in newly diagnosed patients with type 2 diabetes mellitus

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Introduction
It has been shown that type 2 diabetes mellitus (T2DM) could affect bone metabolism through several mechanism and it may increases risk for osteoporosis. Glucose lowering therapies including metformin has also been reported to may effect on bone turnover. This study aimed to evaluate the effects of metformin therapy on bone resorption and formation markers in newly diagnosed patients with T2DM.
Method/design
Study population consisted of 37 newly diagnosed patients with T2DM. Fasting plasma glucose (FPG), post prandial plasma glucose (PPG), HbA1c, Ca, P, PTH, osteocalcin and type 1 collagen C-telopeptide (CTX) levels were measured before and after 3 months metformin therapy period.
Results
Metformin therapy significantly decreased osteocalcin, which is biomarker of bone formation, in female patients. Metformin therapy also decreased CTX, which is biomarker of bone resorption, in these patients. But this decrease was not statistically significant (Table 1). There was no significant change in Ca, P and PTH levels after metformin therapy.
Conclusions
Our results indicate that metformin therapy may impair bone formation by decreasing bone formation in patients with T2DM. Further controlled, long term studies are needed to clarify clinical importance of these findings.

Table 1 Metformin therapy on bone resorption and bone formation markers.

	Before therapy	After therapy	*P* values
CTX (ng/ml)	297±187.9	272±196.8	0.23
Osteocalcin (ng/ml)	6.23±5.52	4.7±3.04	<0.05

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The favourable effects of autologous hematopoietic stem cell transplantation on the immune system in patients with type 1 diabetes

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Objective
Autologous hematopoietic stem cell transplantation (AHSCT) is a promising treatment to reverse type 1 diabetes (T1D) in patients with significantly improved β-cell function. This study was designed to investigate the potential immunological mechanisms involved.
Design and methods
18 newly-diagnosed T1D were divided into two groups, the AHSCT group and the insulin therapy group. Blood mononuclear cells (PBMCs) of the patients at the baseline visit and the 12-month follow-up time was collected and cultured. Cell proliferation study was assessed by cell count kit 8 (CCK8), proportion of T cell subsets were analyzed by flow cytometry, and the concentrations of the cytokines in the cell culture supernatants was detected by Procarta Immunoassay Kit. The mRNA expressions of the cytokines were tested by real-time PCR.
Results
i) PBMC showed significant lower proliferation in the AHSCT group and the insulin therapy group compared to the newly-onset group, no difference was found between the two treatments; ii) the proportion of Th1 and Th17 cells decreased in the AHSCT group, but no change was found in the insulin therapy group compared to the newly-onset group; the mRNA expression of IL2 and IFNγ and the supernatants concentrates were significantly reduced in the AHSCT group, while the same levels were found in the insulin therapy group as the newly-onset group; and iii) The proportion of Treg cells in the AHSCT group was close to the newly-onset group, while it changed less in the insulin therapy group, accompanied with the up-regulated mRNA expression and the increased supernatants concentrations of TGF-β in the AHSCT group compared to newly-onset group. No difference was found in the insulin therapy group.
Conclusion
Our results suggested that the AHSCT treatment has induced a favorable immune situation by reducing activity of PBMC proliferation, associated with skewing from Th1/Th17-dominated to increased Treg phenotypes. It might be important to normal immunity and disease control.

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The effect of continuous subcutaneous insulin infusion therapy on acute complications and pregnancy outcome in pregnant women with type 1 diabetes mellitus

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Background and aims
Fetal, maternal and perinatal complications are increased in pregnant women with type 1 diabetes mellitus (T1DM). In this study, we aimed to evaluate the effects of CSII on pregnancy outcomes, glycemic control and acute complications in pregnant women with T1DM.
Materials and methods
We retrospectively analyzed the data of women with T1DM, who were on CSII therapy during their pregnancy, followed at our clinic between 2008 and 2012. We examined 15 pregnant women with T1DM, five of whom were already on CSII therapy before pregnancy and ten patients who were swiched from MDI to CSII therapy at the beginning of their pregnancy due to frequent hypoglycemic and hyperglycemic attacks. Acute complications, fetal/maternal and perinatal complications and glicemic control were analyzed.
Results
The mean age of the patients was 28.2±3.6 years and the mean duration of diabetes was 8±5.4 years. Severe hypoglycemic episode and diabetic ketoacidosis were not observed during their pregnancy. The mean HbA1c at the beginning of pregnancy fell from 7.4±1.3 to 6.3±0.7% before delivery. The mean duration of pregnancy and neonatal birth weight were 37.1±1.2 weeks and 3537±794 g respectively. There were no stillbirths, perinatal infant deaths or congenital malformations. There were two preterm births due to preeclampsia, one of whom had a low birth weight (1800 g). One macrosomic baby with a birth weigt greater than 4500 g was recorded. Pre-pregnancy and before-delivery mean HbA1c values were not associated with neonatal birth weight or preterm delivery.
Conclusion
In our study, glycemic control improved with CSII therapy during pregnancy. However, despite a significant improvement in their HbA1c levels, the patients still had higher HbA1c than target values, which could be explained by selection of a population with hard-to-control glycemia. Severe hypoglycemia or diabetic ketoacidosis were not detected in our study. We conclude that in pregnant women with T1DM of whom glycemic control could not be achieved with MDI therapy, CSII therapy is a safe and appropriate treatment regimen to provide well glycemic control.

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Effect of omega-3 polyunsaturated fatty acids on insulin resistance in type 2 diabetes

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Background
Omega-3 polyunsaturated fatty acids are found in fish oil and they have been shown to mitigate the risk of cardiovascular disease. The mechanisms of which are not only improvement of triglycerides and various lipid parameters, but also

beneficial effects on arrhythmia, inflammation. There are animal experimental results that omega-3 fatty acid can improve insulin resistance related to obesity and non-alcoholic steatohepatitis. The mechanism can be activation of PPAR-r related to insulin sensitivity, GLUT2 and GLUT4 related to glucose transport, IRS1 and IRS2 related to insulin receptor. Anti-inflammatory effect and inducement of AMPK phosphorylation that is important in energy metabolism can also contribute to the mechanism of improving insulin resistance. But studies about its effects on insulin resistance are limited and the results were not consistent. So, we compared the change of insulin resistance after omega-3 polyunsaturated fatty acids treatment in type 2 diabetes.
Method
We recruited 180 type 2 diabetic patients whose triglyceride level was above 200 mg/dl during the anti-diabetic medication. They were prescribed 2000 mg/day of omega-3 polyunsaturated fatty acids without changing of other medication. HOMA-IR level before and after medication was compared.
Results
HOMA-IR was improved by 3.06 ± 1.73 in 56% (100/180) of patients and aggravated by -2.55 ± 3.87 in 44% of patients. The mean change of HOMA-IR in whole group was 0.57 ± 3.89. The change of HOMA-IR was independent of improvement in triglyceride level or other factors such as BMI, HgA1c level, duration of diabetes.
Conclusion
Omega-3 polyunsaturated fatty acids treatment in type 2 diabetes has no effect on insulin resistance by HOMA-IR measurement.

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Inhibition of SGLT using $Ca^{2}+$-zeolite and preserve the periphery of glucose excess

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Diabetes mellitus (diabetes) can now be called the disease of modern times due to its increasing incidence especially in the more developed parts of the world. It is characterized by the inability of the body to produce and/or properly use insulin. In our work we engaged in research of type 1 diabetes in NOD animal model. The focus of our study was relatively recently discovered SGLT time in the small intestine, which are actively inhibited by Ca^{2+} zeolite. SGLT1 transporter is Na^{+}/glucose koransporter located in the small intestine and the small amount in the kidney.
The mice are divided into three main groups: two control diabetic (diabetic who received insulin and diabetic receiving insulin+probe with Ca^{2+}-zeolite). Animals were tested for the ability of current glucose tolerance test glucose tolerance. Then, in order to determine the direct effect of the application of the Ca^{2+}-zeolite concentration of glucose at normal physiological conditions, the test animals were used to determine the concentration of glucose in the peripheral blood after feeding. Results in both cases showed significantly better glucose regulation in the group of diabetic mice which received the probe with Ca^{2+}-zeolite compared to the diabetic group that received the physiological solution. We then incubating small intestine *in vitro* followed the Na/Ca exchange in order to check whether the activity goes beyond the presumed active glucose transport. How to track metabolic changes in the treated mice were placed for 24 h in the metabolic cages after 14-day of treatment. The results showed a clear difference in the amount of urine excreted between the two diabetic groups. Finally, to monitor the in vivo process of glucose, all three groups of animals were recorded and are microPET camera and the results clearly showed accumulation of glucose in animals treated with Ca^{2+}-zeolite.
Results of this study clearly demonstrate the positive impact of the application of Ca^{2+}-zeolite in combination with insulin in the regulation of hyperglycemia (and thus in the prevention of late complications).

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Efficacy of acarbose in different geographical regions of the world: analysis of a real-life database

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Introduction
Although alpha-glucosidase inhibitors (aGIs), including acarbose, are recommended in several international guidelines, they are not widely used worldwide due to a perception that they are less effective in Caucasians than Asians. A study was undertaken to investigate whether differences between ethnicity/region populations exist.
Methods/design
We pooled data from 10 non-interventional and post-marketing studies from 21 countries, provinces and country groups from the launch of acarbose to 2011. The effects of acarbose on glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose (FPG) and post-prandial plasma glucose (PPG) were analyzed for four major ethnicity/region groups: Caucasians from Europe and Asians from East, South East and South Asia.
Results
The efficacy population included 62,905 patients, with 59,090 patients from the four groups of interest. At the 3-month visit, mean HbA_{1c} had decreased by $-1.12 \pm 1.31\%$ from 8.4% at baseline ($n=32,692$), FPG by 37.59 ± 47.26 mg/dl from 170.2 mg/dl ($n=45,102$), and PPG by 70.00 ± 65.30 mg/dl from 238.2 mg/dl ($n=43,290$) ($P<0.0001$ for all comparisons). Reductions in HbA_{1c}, FPG and PPG were larger in patients with higher baseline values regardless of ethnicity and region. Data from 30,730 patients from the four groups with non-missing baseline and 3-month HbA_{1c} data, age and sex were analyzed by multivariable ANCOVA. After adjustment for relevant baseline confounding factors, South East and East Asians had slightly better responses to acarbose than South Asians and European Caucasians; however, the differences were numerically small (e.g. relative difference of $\sim$2.2% for baseline HbA_{1c} of 7.2%; $\sim$3.4% for baseline HbA_{1c} of 9.2%). In the safety population ($n=67,682$), acarbose was well tolerated, with few episodes of hypoglycemia (0.03%) and gastrointestinal adverse events (2.76%).
Conclusion
Acarbose was effective in European Caucasians and Asians; however, after adjustment for baseline confounding factors, South East and East Asians had slightly better responses to acarbose than South Asians and European Caucasians.

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Evolution of ambulatory blood pressure monitoring in a cohort of patients with type 1 diabetes after 7 years

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Objective
To evaluate changes of ambulatory blood pressure monitoring (ABPM) parameters in normotensive and normoalbuminuric patients with type 1 diabetes (TDM1) after 7 years.
Methods
A longitudinal study conducted in normotensive and normoalbuminuric patients with TDM1. ABPM (Spacelabs 90217) basal was performed. Altered ABPM was considered when: i) Mean systolic pressure (sBP) was $\geq$130 mmHg in the 24 h and daytime periods and $\geq$120 mmHg in the night-time period and/or mean diastolic pressure (dBP) $\geq$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, and/or iii) nocturnal fall in either sBP or dBP was lower than 10%

(non-dippers). Patients meeting criteria 1 or 2 were considered hypertensives and treated with an ACE inhibitor (Enalapril). Patients were reevaluated after 7 years.
Results
Sixty-nine patients (52.2% women) were included, aged 28.3±6.1 years and 11.4±6.2 years of diabetes evolution. 17 patients (24.6%) were diagnosed as hipertensive and were treated. No clinical differences were detected between groups (age, diabetes evolution, BMI, and HbA1c). After 7 years there was a significant improvement in mean daytime sBP (from 131.4 ± 8.8 to 124.4 ± 10.9 mmHg, $P<0{,}001$) and night-time sBP (from 113.6 ± 11.8 to 108.4 ± 10.5 mmHg, $P<0{,}001$) among treated patients. Among basal normotensive patients, although no relevant changes were detected in ABPM parameters, four patients (7.7%) developed hypertension. No differences in retinopathy or nephropathy prevalence were detected between groups in the basal and final evaluation.
Conclusions
In our study, treatment with ACE inhibitors improves ABPM parameters in hypertensive patients; normotensive patients rarely progress to hypertension after 7 years of evolution.

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P497

The evaluation of the long-term effect of insulin pump therapy in children with type 1 diabetes mellitus

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Introduction
CSII is considered to be a more comfortable therapy and provide the best glycemic control. However, studies concerning of the long-term effects of pump therapy yield conflicting results, some of them reported beneficial long-term effect on metabolic control (reduction of HbA1c), whilst others have shown effects for a short period of time, not exceeded 1 year.
The aim of the study was evaluation of the long-term effect of insulin pump therapy on metabolic control in children with type 1 DM.
Methods
46 children with type 1 DM from 4.2 years, mean age 12.5±2.7 years, mean HbA1c 8.4±1.6 entered the study. The total patient population was divided into two groups based on the age at the start of pump therapy: group A, 4–10 years old and group B, 11–18 years old. Anthropometric data (age and BMI), HbA1c, and insulin requirement have been evaluated at baseline (at the start of CSII therapy) and every 6 months intervals for 5 years during pump therapy.
Results
At baseline, the mean HbA1c level was 8.68 in the group of younger children and 8.22 in the group of older children. In both groups of patients, significant ($P<0.05$) improvement of the HbA1c level was shown only during the first 6 months of observation, 6.9 and 7.1 respectively with gradual deterioration in subsequent years, up to the level of HbA1c 8.11 and 8.56 respectively.
No significant difference has been shown concerning BMI, insulin requirement, DKA episodes from baseline throughout the follow-up.
Conclusions
Our study has shown that insulin pump therapy helped achieve lower HbA1c in a relatively short period of time. Interestingly, in the group of the younger children, the metabolic control was slightly better. It seems that better parental control of the younger children may influence the observed differences in the HbA1c level.

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P498

Insulin infusers: 8 years experience

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Objective
To evaluate the response to treatment with insulin infusion pumps by the evolution of HbA1c over 8 years of experience.
Methods
Observational retrospective study. We evaluated the response to treatment in 122 patients with type 1 diabetes recruited between 2004 and 2012 in our area.
Results
Between 2004 and 2012, 122 pumps have been implemented (average of 17.4 pumps/year). The number decreased to only four in 2012. Prescription indications were: glycemic instability (14.7%), poor metabolic control (44%), hypoglycemia (18%), pregnancy (9%) and pregnancy planning (12.3%). There have been 13 dropouts (10.6%): no adaptation to therapy (38.4%), poor compliance and poor control (30.7%), no improvement (23%) and termination of pregnancy (7.7%). During the 1st year we observed a decrease in mean HbA1c of 0.7%, maintained in the second year and beyond, ranging between 0.6 and 0.5% in the 5th year of follow-up ($P<0{,}05$). In patients with poor metabolic control, HbA1c improvement is proportionally higher, ranging from 9.6 to 7.7% prior to year 6 ($P < 0.05$). There is a decrease in HbA1c at baseline (0.4%) due to the education program received ($P < 0.05$). The percentage of patients with better HbA1c than at baseline decreases as the years pass, from 97% the 1st month to 75% after the first year and 50% at 6 years of treatment.
Conclusions
This therapy has been effective in most patients. For better results an appropriated selection of candidates is required.The decrease in HbA1c is more pronounced in the first months of treatment and has already started before the implantation of the insulin pump, probably by the intensive educational program received.

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P499

Differential effects of native Peptide YY and its long acting analogue (Y-59) on innate lymphocyte function and anti-tumour activity

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Background
Peptide-YY is synthesised and secreted by specialised cells in the ileum and colon. Levels increase following food intake, having a satiety effect. Baseline and postprandial levels of PYY were found to be lower in obese subjects compared to lean, negatively correlating with the subjects BMI, however obese subjects were sensitive to the anorectic effects of PYY when given exogenous PYY.
Hypothesis
We have recently demonstrated that another prandial gastrointestinal hormone, glucagon-like peptide 1 (GLP 1), is immunomodulatory and has therapeutic effects in inflammatory disease. We proposed that PYY would play a role in regulating human natural killer (NK) and invariant natural killer T (iNKT) cells.
Methods
We looked for the presence of a functional PYY on iNKT cells and the downstream transcription factors. We investigated the *in vitro* effects of PYY and a long acting PYY analogue Y-59 treatment on iNKT cell function (cytokine production and tumour cell lysis). Finally we examined the direct anti-tumour activity of Y-59 treatment (tumour cell growth and colony formation).
Results
Activation with PYY and its analogue Y-59 resulted in modest modulation of iNKT cell cytokine production with inhibition of IFN-γ ($P<0.05$) secretion but not IL4 ($P=0.7$). Both PYY and Y-59 significantly increased iNKT cell and NK cell cytolytic degranulation *in vitro*. The long acting PYY analogue Y-59 reduced tumour cell growth ($P<0.01$).
Conclusion/interpretation
PYY displays immunomodulatory/anti-tumour effects via its actions on human iNKT and NK cells and direct effects on tumour cell growth. This suggests that the gastrointestinal hormone system produces immunomodulatory peptides, which may be targeted in obesity related diseases such as cancer.

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P500

Liraglutide effects on glycaemic control, body weight, blood pressure and lipid profile in obese patients with type 2 diabetes: real-life clinical practice

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Objective
To evaluate the efficacy of liraglutide, a new glucagon-like peptide 1 analogue, on glycaemic control, body weight, blood pressure and lipid profile in obese patients with type 2 diabetes mellitus (T2DM).
Material and methods
Patients attending a tertiary Endocrinology Unit who were prescribed liraglutide (January 2013–December 2013) and assessed both at baseline and first post-initiation visit were included in the analysis. The primary endpoint was change in HbA1c from baseline. Body weight, blood pressure, lipid profile, adverse effects and frequency of hypoglycaemic events were also assessed.
Results
48 obese (mean weight 106.9 ± 19 kg and mean BMI 39.8 ± 5.1 kg/m^2) type 2 diabetic patients (mean age 53.6 ± 10.4 years and men 43.8%), started treatment with liraglutide in the study period. Mean baseline HbA1c was 8.6 ± 1.2%, mean baseline systolic blood pressure (SBP) levels were 150.3 ± 19.3 mmHg and diastolic blood pressure (DBP) were 86.9 ± 10.6 mmHg. Baseline concentrations of total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides were 190 ± 45.3, 41.6 ± 11.5, 112.2 ± 36.6 and 266.1 ± 194.6 mg/dl respectively. Average time to first visit after liraglutide initiation was 18.6 weeks. Mean change in HbA1c from initiation to first visit was −1.3%, while mean body weight change was −3.4 kg, and change in SBP was −10.5 mmHg (P for all <0.005). No changes in lipid profile or DBP were found. Mild transient gastrointestinal side effects were experienced by 18.4% of patients. None patient discontinued liraglutide treatment or reported hypoglycaemia.
Conclusion
In real-life clinical practice, addition of liraglutide in patients with T2DM inadequately controlled improves glycaemic control, decreases body weight, and lowers blood pressure.

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P501

Is there a relationship between body composition and insulin regimen modality in type 1 diabetic patients?

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Introduction
Diabetes is characterized by an increase in abdominal fat. This results in a decrease in lean body mass and increase in insulin resistance. In this study, we aimed to evaluate the possible relationship between body composition and insulin regimen modality in type 1 diabetic patients.
Materials and methods
Ninety-two type 1 diabetic patient followed in our institution were included in the study. Patients were classified into two groups according to the type of insulin regime; multiple dose insulin injection (MDI) and insulin pump therapy (CSII). Sex and age of the patients and each of fasting plasma glucose (FPG), total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol and HbA1c levels were recorded. BMI, waist-to-hip ratio and waist-to-height ratio were calculated. Body composition analysis were done with bioelectric impedance analysis method and body fat percentage, total body water, fat mass and fat-free mass were recorded. Differences in demographic data, anthropometric measurements and biochemical parameters, among MDI and CSII groups were evaluated.
Results
Forty-one of the patients were male. Sixty-one patient constituted the MDI group and the resting 31 the CSII group. When the two groups were compared according to age, FPG, lipid parameters and HbA1c; only FPG was found significantly different. There were no significant differences in any of the anthropometric measurements among two groups.
Conclusion
In our study, FPG was significantly lower in the CSII group while HbA1c did not show any significant difference among groups. Body composition parameters were found to be similar among two groups. Preferential fat accumulation in abdominal region may harden the insülin regimen and worsen the glysemic control especially in the CSII treatment group. But in our study HbA1c values were comparable among two groups. Studies with larger patient numbers may help to demonstrate this possible difference among this two treatment groups.

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Endocrine disruptors

P502

Acute exposure of BPA from electronic gadgets does not induce oxidative stress in the rat's brain

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Objective
To investigate the effects of BPA on oxidative damage in terms of activity level of antioxidant enzymes in different regions of the rat brain.
Background
The ever increasing uses of electronic gadgets are becoming a widespread source of bisphenol-A accumulation. As studies have been reported that low level BPA accumulation may produce neurological effects but still limited studies have re-examined for its adverse effects in terms of acute exposure from electronic devices.
Methodology
In this study, BPA migration was estimated through physio-chemical parameters and leachate (equivalent to 4 mg/kg body weight) was used for animal dosing. Three groups of Albino Wister rats (190 ± 20 g) were used for control, sham, and treated. The antioxidant enzymes including superoxide dismutase (Mn-SOD), catalase (CAT), glutathione peroxidase (GPx) and reduced glutathione level (GSH) were measured in different brain regions, i.e. corpus striatum, frontal cortex, thalamus and midbrain.
Results
No significant changes were observed in most of the brain regions yet the level of GPx activity in corpus striatum (29.65 ± 0.98 nmol/min per mg protein) and level of GSH activity in frontal cortex (2.33 ± 0.12 µmol/g protein) was found to decrease significantly ($P<0.05$) when compared to controls. In addition, no significant effects were observed for the oxidative damage in brain regions of sham group when compared to control group.
Conclusion
Thus study suggests that acute exposure (4 mg/kg body weight per day up to 28 days) of BPA does not induce significant oxidative damage in the rat's brain. Furthermore, study might re-examine before affirm the final remark for subscribers and regulatory bodies at similar doses.

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P503

The reproductive toxicity of butyl benzyl phthalate in male rabbits: the possible protective role of flaxseed

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The present study was carried out to investigate the reproductive toxicity of butyl benzyl phthalate (BBzP) on semen characteristics, hormones levels (testosterone,

LH and FSH), testicular lipid peroxidation and antioxidants enzymes and histological changes in testes in male rabbits for 12 weeks. The flaxseed lignan and its mammalian metabolites have been reported to exert protective effects against diet-related chronic diseases through a variety of mechanisms including phytoestrogenic and antioxidant effects. Therefore, the protective effect of flaxseed against BBzP-induced reproductive toxicity and oxidative stress was studied. Rabbits were orally administered the doses of flaxseed, BBzP and flaxseed plus BBzP every day for 12 weeks. Results obtained showed that BBzP significantly decreased libido, ejaculate volume, sperm concentration, total sperm output, sperm motility, total motile sperm per ejaculate, packed sperm volume, total functional sperm fraction, normal and live sperm and semen initial fructose. While, FSH, LH, initial hydrogen ion concentration (pH), and dead and abnormal sperm were increased. Also, testosterone levels, body weight (BW), relative weights of testes (RWT) and epididymis (RWE) were decreased. Thiobarbituric acid-reactive substances and lactate dehydrogenase were increased, while antioxidant enzymes, transaminases and phosphatases were decreased in seminal plasma of rabbits treated with BBzP compared to control. Flaxseed alone significantly increased testosterone levels, BW, RTW, REW, improved semen characteristics and seminal plasma enzymes, and decreased the levels of free radicals and lactate dehydrogenase. Furthermore, the presence of flaxseed with BBzP alleviates its toxic effects. From the present study, it can be concluded that flaxseed can be effective in the protection of BBzP-induced reproductive toxicity.

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P504

Treatment with kaempferol resulted in the regulation of cell cycle-related and apoptosis-related genes in cancer cell growth caused by triclosan in MCF-7 breast cancer cells

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Triclosan is one of endocrine-disrupting chemicals (EDCs) which are scattered with environment agents, such as toothpastes, deodorant and cleaning supplies. As a phytoestrogen, kaempferol is one of bioflavonoids, which has been found at variety of vegetables including broccoli, tea and tomato. Although kaempferol may have anti-cancer activity, its exact mechanism is under investigation in the induction of apoptosis and inhibition of cell proliferation or angiogenesis. In this study, we examined the anti-proliferative effects of kaempferol in triclosan-induced cell growth in MCF-7 breast cancer cells. A proper concentration of kaempferol or triclosan was determined in MCF-7 cells measured by MTT assay. In this study, kaempferol significantly reduced the viability of MCF-7 cells compared to a negative control treated with DMSO, and that kaempferol reversed triclosan-induced MCF-7 cell growth at 50 μM. To confirm that kaempferol inhibited triclosan-induced cell growth, we examined the transactional levels of cell growth and apoptosis-related markers, i.e. cyclin D, p21, cyclin E, p27 and bcl-2, and bax genes, using RT-PCR. The expression levels of cyclin D, cyclin E and bax/bcl-2 ratio were increased, while that of p21 and p27 mRNAs was decreased by triclosan in MCF-7 cells. In addition, kaempferol reversed triclosan-induced gene expressions in an opposite manner. In parallel with its mRNA level, the protein level of cyclin E was induced by triclosanm while it was reversed by kaempferol as shown by western blot analysis. Taken together, these results indicated that kaempferol may inhibit the growth MCF-7 cells via regulating of cell cycle and apoptosis-related genes. In addition, EDCs-induced progression of breast cancer may be suppressed by a phytoestrigen, i.e. kaempferol, in a specific manner.

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P505

Treatment of prostate cancer cells with phthalate resulted in the upregulation of cyclin D1 and c-myc and downregulation of p21 via estrogen receptor signaling pathway in the progression of LNCaP prostate cancer cells

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The distinct roles of estrogen receptors (ERs) related with androgen receptors (ARs) have been proposed in prostate cancer, while the involvement of transforming growth factor-β (TGF-β) has been reported in prostate cancer progression. We examined that TGF-β signaling pathway is associated with ER signaling in LNCaP prostate cancer cells, which express ERα and ERβ, and ARs. We determined whether the exposure to phthalate may induce the prostate cancer progression by affecting molecular crosstalk between ER and TGF-β signaling pathways. Cell viability was measured in LNCaP cells by MTT assay following treatment with di-*n*-buthyl phthalate (DBP). RT-PCR and immunoblot assay were performed to examine the expression levels of cell cycle related genes and TGF-β signaling cascade. A mouse xenografted model of prostate cancer was generated, and immunohistochemical and BrdUrd assay were carried out to determine the effect of DBP in this mouse model. DBP was shown to promote LNCaP cell proliferation by upregulating gene expression of c-myc and cyclin D1 and by downregulating p21 expression. These regulations caused by DBP were reversed by ICI 182 780, indicating that DBP may affect the crosstalk between TGF-β and ER signals. In *in vivo* mouse model, tumor volume of mice exposed to DBP was increased. Number of cells in S phase of cell cycle was increased by DBP, while expression of p21 protein was reduced in the tissues of DBP-treated mice. These results indicate that DBP may induce the growth of prostate cancer by acting on crosstalk between TGF-β and ER signaling pathways.

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P506

Treatment of breast cancer cells with triclosan and octylphenol altered the expressions of cyclin D1 and p21 and induced breast tumor masses via an estrogen receptor-dependent signaling pathway in cellular and mouse xenograft models

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In the present study, we determined whether two endocrine-disrupting chemicals (EDCs), triclosan (TCS) and octylphenol (OP), are able to alter the expression of two cell cycle regulators, cyclin D1 and p21, in both *in vitro* and in mouse breast cancer models. In addition, we determined whether the stimulatory effects of OP or TCS on breast cancer progression may be associated with an estrogen receptor (ER)-mediated signaling pathway. Altered expressions of cyclin D1 and p21 were observed in MCF-7 human breast cancer cells treated with TCS and OP. These disruptions were linked to the control of the G1/S transition during carcinogenesis. In a xenograft mouse model, breast tumor masses were established following exposure to TCS and OP for 8 weeks. In these animals, the growth of tumor cells with BrdU-positive nuclei was by treatment with 17β-estradiol (E_2), OP, and TCS compared to a control (corn oil), suggesting that TCS and OP increase DNA synthesis during the S phase in tumor cells. Amplification of cyclin D1 by TCS and OP was also observed *in vivo*, implying that the effects of these EDCs possessing estrogenic activity alter the expression of genes related to cancer progression. It was of interest that the effects of TCS and OP were reversed by ICI 182 780, an ER antagonist, indicating that EDC-induced activities are mediated by an ER-dependent signaling pathway. Taken together, these results suggest that TCS and OP can adversely affect human health, i.e. by promoting breast cancer progression, via an ER-mediated signaling cascade.

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P507

Transcriptional levels of aryl-hydrocarbon receptor, aryl-hydrocarbon receptor dependent- and cell cycle-related genes were altered by fenhexamid in human ovarian cancer cells expressing estrogen receptors

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Fenhexamid is one of antifungal agents used in agricultural applications, which are present at measurable amounts in fruits and vegetables. Fenhexamid has been reported to act as an anti-androgen in an androgen receptor reporter assay in engineered human breast cancer cells. Aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor, which translocates into nucleus and

dimerizes with aryl hydrocarbon receptor nuclear translocator (ARNT). Although function of ARNT is not clear, AhR–ARNT complex appears to be regulated by AHR response element (AHREs), dioxin-responsive element (DRE) or xenobiotic responsive element (XRE). In this study, we examined the effects of fenhexamid, a pesticide, on the expressions of AhR, CYP1A1, CYP1B1, ARNT, and p21 by RT-PCR analysis. In addition, the cell viability by fenhexamid was examined in BG-1 human ovarian cancer cells by MTT assay. To evaluate the ability of cell viability, BG-1 cells were cultured with a negative control (0.1% DMSO), 17β-estradiol (E_2; 1×10^{-9} M), 2,3,7,8-tetrachlorodibenzo-ρ-dioxin (TCDD; 1×10^{-8} M), or fenhexamid (1×10^{-5} to 1×10^{-8} M). E_2 as a positive control markedly increased BG-1 cell proliferation compared to DMSO. In addition TCDD and fenhexamid increased BG-1 cell proliferation at the concentration of $1\times10^{-}8$ and 1×10^{-5} M respectively. The transcriptional level of p21 was reduced at 6 h by E_2, TCDD, or fenhexamid, while its level was reversed at 24 h following their treatments. The mRNA expression of AhR was reduced by E_2, TCDD, or fenhexamid in a time-dependent manner, while its level was reversed in the presence of alpha-naphthoflavone, an AhR inhibitor. In contrast, the transcriptional level of ARNT appeared to be increased by E_2, TCDD, or fenhexamid. Taken together, these results indicate that fenhexamid may regulate AhR, ARNT and p21 to induce cell growth in BG-1 ovarian cancer cells expressing estrogen receptors. A further study will continue to examine disruptive effects of pesticides in estrogen receptor expressing cells or tissues.

Keywords: Pesticides, TCDD, fenhexamid, endocrine disrupting chemicals, ovarian cancer, aryl-hydrocarbon receptor

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P508

Transcriptions of cell cycle-related genes were altered by benzylbutyl phthalate and diisobutyl phthalate via an estrogen receptor α signaling pathway in human ovarian cancer cells

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Phthalates are mainly used as substances added to plastics for increase flexibility, durability and transparency. Although phthalates have been reported to act as endocrine-disrupting chemicals (EDCs) and appear to cause detrimental effects on human health, diverse cancers and diseases, exact effect(s) and underlying mechanism(s) remain uncovered. The estrogenic activity of EDCs is partially associated with ability to stimulate cell viability in estrogen-dependent cancers expressing estrogen receptors (ERs), i.e. breast and ovarian cancers. 17β-estradiol (E_2) as endogenous estrogens is an important factor in tumor growth and progression of estrogen-dependent diseases. In this study, we examined the effects of diverse phthalates, i.e. benzylbutyl phthalate (BBP) and diisobutyl phthalate (DiBP), on the expressions of cell cycle genes, i.e. p21, cyclin D1, and ER-α by RT-PCR analysis. In addition, the cell viability effect of phthalates was examined in BG-1 human ovarian cancer cells by MTT assay. To evaluate the ability of phthalates on cell proliferation, BG-1 cells were cultured in media added with negative control (0.1% DMSO), positive control (E_2 1×10^{-9} M), BBP and DiBP (1×10^{-5} to 1×10^{-8} M). As a positive control, E_2 markedly increased BG-1 cell proliferation compared to DMSO. Also BBP increased BG-1 cell proliferation at 1×10^{-5} and 1×10^{-6} M dose. In addition, DiBP increased BG-1 cell proliferation at 1×10^{-5} M dose. These results demonstrated that phthalates promotes the proliferation of BG-1 human ovarian cancer cells similar to E_2. In addition, the expression levels of cell cycle related genes, p21, cyclin D1, and ER-α, were determined by RT-PCR. E_2, BBP and DiBP decreased the expression levels of p21 and ER-α mRNAs in a time-dependent manner (0, 6 and 24 h), while the expression level of cyclin D1 mRNA increased. In this study, protein levels of p21, cyclin D1 and ER-α are being examined at the moment, and *in vivo* animal study is being studied to examine disruptive effects of phthalates on endocrine and reproductive systems.

Keywords: Phthalates, endocrine-disrupting chemicals, ovarian cancer, cell cycle gene, estrogen receptor-α.

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P509

Estrogen and bisphenol A affect enamel formation by different signaling pathways

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Bisphenol A (BPA) is a widespread endocrine disrupting chemical strongly suspected to have adverse health effects. Numerous tissues and cells are affected by BPA, and we showed recently that BPA targets include ameloblasts and enamel. We therefore investigated the effects of BPA on ameloblasts and the possible involvement of the estrogen signaling pathway. Rats were exposed daily to low-dose BPA from the conception to 30 days after birth (30 D). Seventy-five percent of 30 D rats exposed to BPA developed enamel hypomineralization similar to human Molar Incisor Hypomineralization (MIH). Ameloblast proliferation was induced by BPA *in vivo* and *in vitro* and could lead to enamel hypomineralization by affecting amelogenesis process. The proliferation of the rat dental epithelial cell line HAT-7 was also increased by estrogen (E_2). Ameloblasts express ERα but not ERβ both *in vivo* and *in vitro*. The ER antagonist ICI 182 780 was used to inactivate ERα and abolished the effects of E_2 on cell proliferation and transcription, but only partially reduced the effects of BPA. In conclusion, we show, for the first time, that: i) BPA has ER-dependent and ER-independent effects on ameloblast proliferation and gene transcription and ii) the estrogen signaling pathway is involved in tooth development and the enamel mineralization process. These results are consistent with the steroid hormones having effect on ameloblasts, raising the issues of the hormonal influence on amelogenesis and possible differences in enamel quality between sexes.

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P510

Organometric parameters of rat's adrenal glands after 60-day administration of sodium benzoate and application of mexidol

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Aim to study the particularities changes of organometric parameters of rat's adrenal glands after 60-day administration of sodium benzoate and justify possible correction of identified changes by application of mexidol.

The study was conducted on 90 mature male rats with an initial weight of 200–210 g, which were divided into three groups: 1st group – control animals, 2nd group – rats that within 60 days daily intragastrically injected 1 ml of sodium benzoate at a dosage of 500 mg/kg, 3rd group – rats that within 60 days daily intragastrically injected 1 ml of sodium benzoate at a dosage of 500 mg/kg and subcutaneously 5% solution of mexidol at a dosage 50 mg/kg. Animals were withdrawn from the experiment on 3 day after the end administration of the sodium benzoate. Using digital calipers, accurate to 0.05 mm measured length, width and thickness of the left and right adrenal glands.

In the animals of 2nd group length of right adrenal gland decreased, as compared with the 1st group, from 3.46 ± 0.04 to 3.00 ± 0.10 mm (13.29%, $P<0.05$), length of the left – from 3.30 ± 0.08 to 2.44 ± 0.02 mm (26.06%, $P<0.05$), and the thickness of the left adrenal gland – from 2.42 ± 0.10 to 2.14 ± 0.07 mm (11.57%, $P<0.05$). In animals of 3rd group length of the right adrenal gland increased, compared with the parameters of the 2nd group, from 3.00 ± 0.10 to 3.96 ± 0.18 mm (32.00%, $P<0.05$), length of the left – from 2.44 ± 0.02 to 3.23 ± 0.15 mm (32.37%, $P<0.05$), the width of the right – from 3.72 ± 0.07 to 4.50 ± 0.08 mm (20.97%, $P<0.05$), the thickness of the right – from 2.40 ± 0.11 to 2.98 ± 0.12 mm (24.17%, $P<0.05$), and the left adrenal gland – from 2.14 ± 0.07 to 2.86 ± 0.14 mm (33.64%, $P<0.05$).

Thus, the 60-day daily administration of sodium benzoate mature animals accompanied by a decrease of the linear dimensions of the adrenal glands and the application of mexidol a at dosage of 50 mg/kg smoothes revealed changes.

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The potential role of bisphenol A in the pathogenesis of polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age, that lead to infertility, type 2 diabetes and coronary heart disease.
Bisphenol A (BPA) is one of the most abundant chemicals produced worldwide and is used as a plasticizer in daily life. Nowadays it is also well know that it can interact with estrogen receptors, androgen receptors and peroxisome proliferator-activated receptors γ (PPARγ). Therefore, the aim of this study was to identify the potential role of BPA in the pathogenesis of PCOS which is the most common endocrinopathy in premenopausal women.
In total 137 women were studied. Sixty-six (mean age 24.5±3.66) were diagnosed with PCOS according to the ESHRE/ASRME (Rotterdam Criteria) consensus. The control group consisted of 71 women (mean age 28.4±4.22) without PCOS. Serum levels of prolactin (PRL), 17OH-progesterone, total testosterone, DHEA-S, insulin and sex hormone-binding globulin (SHGB) were measured. BPA concentrations were analysed in all women's sera using HPLC method combined with mass spectrometry (HPLC-MS/MS analysis, The Agilent 1200 HPLC system). The results of the analysis have pointed to the higher levels of BPA in the sera of women with PCOS in comparison with healthy controls (median: 3.18 vs 1.73 ng/ml, $P=0.05$). There has been a positive correlation between the serum concentration of BPA and total testosterone level ($P=0.004$, $R=0.56$). There were no correlations between serum BPA concentrations and waist circumference, BMI and serum PRL, DHEA-S, insulin.
These results confirmed the hypothesis of higher levels of BPA in PCOS women, that can exacerbate the androgen production.

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Bisphenol A disrupts seminoma cell proliferation following an inverted U-shaped non monotonic dose–response curve, due to its greater affinity for GPR30, the non classical membrane G protein-related estrogen receptor, than for ERβ

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Introduction
Testicular germ cell tumours are the most frequent cancer of young men. Epidemiological and clinical data have suggested that fetal or perinatal exposure to environmental endocrine disruptors (EEDs) with estrogenic effects, could participate to testicular germ cell carcinogenesis. However, EEDs (like bisphenol A (BPA) are often weak ligands for classical nuclear estrogen receptors.
Using a human seminoma cell line (JKT-1), devoid of ERα, we previously reported that low doses of estradiol (E_2; 10^{-9} M) inhibited cell proliferation through classical ERβ. At the opposite, BPA, at the same concentration, could induce cell proliferation through a non classical membrane G-protein coupled estrogen receptor (GPER/GPR30).
Methods
We carried JKT-1 cell proliferation assays with various doses of E_2 and BPA, with or without selective agonists and antagonists of ERβ (ZU, ICI) and GPER (G1, G15), in order to determine the affinity of BPA for ERβ and GPER.
Results
Using selective agonists and antagonists, we confirmed in our model that E_2 had a greater affinity for ERβ than for GPER, with a maximal effect at the concentration of 10^{-9} M. At the opposite, BPA exhibited a greater affinity for GPER than for ERβ, with a maximal effect at the concentration of 10-9M. The response of JKT-1 seminoma cells to E_2 (from 10-5 to 10-12 M) followed a U-shaped nonmonotonic dose response (NMDR) curve. Interestingly, they responded to BPA in the opposite direction, following an inverted U-shaped NMDR curve, which could be totally shifted from top to bottom in case of coexposition to BPA and E_2.
Conclusion
In our model, BPA promotes seminoma cell proliferation at low doses (environmentally relevant) because it exhibits a greater affinity for GPER than for ERβ, explaining the inverted U-shaped NMDR curve observed.

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Di-ethylhexyl-phthalate is metabolised by human thyroid cells and may influence thyroglobulin secretion

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Introduction
Phthalates are suspected to influence thyroid function in epidemiologic and experimental animal studies. The aim of the study was to investigate the ability of primary human thyroid cell cultures to metabolise phthalates and a possible concentration-dependent response of phthalates on thyroglobulin (Tg) secretion.
Methods
Human thyrocytes obtained from thyroidectomies were cultured to confluent monolayers. These were exposed to DEHP in concentrations 10^{-9} to 10^{-4} M, with TSH (1 IU/l) for 24, 48 or 72 h. DEHP metabolites and Tg were quantified in the cell supernatants (liquid chromatography–tandem mass spectrometry and ELISA respectively). Results are shown as mean±S.D. and statistical analyses were performed using two-way ANOVA (SAS Institute).
Results
Cell cultures metabolised DEHP ($10^{-7}-10^{-4}$ M) to its primary metabolite mono-ethylhexyl-phthalate (MEHP). The conversion analysed as metabolite concentration after 72 h exposure varied depending on the DEHP-concentration added, from 1.2±0.6% at 10^{-4} M, to 72.8±21.2% at 10^{-7} M DEHP (n=three cultures from one individual).
No influence was found on TSH-stimulated Tg-secretion after 72 h DEHP exposure (10^{-9} to 10^{-4} M) ($P=0.86$, $n=$ five cell cultures in single determination) compared to controls and independent of the concentration of DEHP used. Preliminary results, however, suggested an inhibitory influence to occur sooner, i.e. after 24 h compared to 48 and 72 h (n=one cell culture in single determination).
Conclusion
DEHP is internalised and metabolised by primary human thyroid cell cultures. The relative conversion, however, decreased inversely proportional to the DEHP concentration added, indicating an active saturable process in the thyroid cells. Preliminary studies indicated a DEHP-mediated decrease in Tg-secretion after 24 h. This finding is currently investigated further. On the other hand, no significant effect on Tg-secretion could be detected after 72 h exposure. Supplementary studies on DEHP-metabolism at earlier time points also need further investigation.

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Endocrine tumours and neoplasia

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Novel and classical molecular pathways identified in pituitary tumorigenesis using mRNA profiling

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Pituitary tumorigenesis has been analysed from multiple perspectives, yet mRNA expression profiling studies are limited. In this study, microarray analysis was used to identify pathways and networks related to pituitary tumour physiology using key de-regulated genes and bioinformatics analysis. Eight pituitary adenomas (five non-functional tumours, two GH-secreting tumours and a TSH/prolactin-secreting tumour) and a pool of random normal control RNA were profiled for RNA expression using the 29 kb Affymetrix HuGene 1.0 ST chip.

Microarray data was analysed using GeneSpring GX 11.0 and network analysis was done using the Ingenuity Pathway Analysis (IPA) software. Data obtained from the microarray was verified on 30 tumours (20 non-functional tumours, six GH-secreting, two prolactinomas and two Cushing's) using quantitative PCR of key genes involved in the networks identified by the IPA. Different analyses between controls and tumour types were carried out. Among the classical networks discovered known to be involved in pituitary tumorigenesis were the cAMP signalling pathway and the Wnt developmental pathway although both networks were driven by genes not previously described in any other study. Different tumour types were also found to be characterised by variable novel de-regulated molecular pathways, such as the GABA signalling and aryl hydrocarbon receptor-signalling pathways in GH-secreting tumours, and the p53 signalling de-regulation in the non-functional tumours. Cluster analysis from microarray data was also able to distinguish between tumour types, identifying one non-functional tumour as belonging to the functional tumours by its mRNA expression profile. This study validates the use for gene expression profiling for the correct characterisation of pituitary adenoma sub-types and identification of key pathways involved in pituitary tumorigenesis thereby proposing possible therapeutic targets.

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Our experience in the evaluation criteria used for the genetic study of patients suspected of being affected by multiple endocrine neoplasia type 1 and mutational spectrum

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Introduction

The autosomal dominant multiple endocrine neoplasia type 1 (MEN1), characterized by parathyroid hyperplasia (PH), neuroendocrine digestive tumours (NET) and pituitary adenomas (PA), is due to mutations in the tumor suppressor gene *MEN1* encoding a 610-amino acid protein, menin. Guidelines recommend *MEN1* mutational analysis in index cases with two or more MEN1-associated tumours, in first-degree relatives of mutation carriers and when clinical data suggest MEN1. We performed *MEN1* genetic analysis in patients referred by Spanish endocrinologists and geneticists from 1997 to 2013. Our aim is to compare our results with inclusion criteria from MEN1 guidelines in order to improve our insight on mutations and phenotype spectrum.

Material and methods

The coding region (exons 2–10), 5′UTR region and intron–exon boundaries of *MEN1* gene were analyzed in 162 index-case patients. When no mutation was thus found, MLPA was performed.

Results

115 (71%) females and 47 (29%) males were studied. Mutations were identified in 56 (35%), 35 females and 21 males; 32 (57%) had familial history of MEN1. 91% presented PH, 55% had NET and 46% had PA. We detected 52 different mutations: 20 frameshift (38%), 18 missense (35%), seven nonsense (14%), six splicing (11%) and one regulatory (2%) mutations; 22 (42%) have not been previously described. Mutations were found in 9/11 (82%) cases with three MEN1-related tumours, 14/38 (37%) with PH and PA, 19/27 (71%) with PH and NET, 0/2 (0%) with PA and NET, 9/59 (16%) with PH, 1/4 (25%) with PA and 4/22 (19%) with NET. 3/9 positive cases with isolated familial PH showed missense mutation.

Conclusions

Our data support current referral criteria for *MEN1* molecular genetic testing. The probability of finding an *MEN1* mutation is correlated with the number of MEN1-related tumours. Patients with PH and NET are more likely to carry a *MEN1* mutation than those with PH and PA. Our data do not suggest that isolated familial PH is associated with missense mutations. *MEN1* mutations were also found in cases with just one tumour, highlighting the importance of analyzing these cases, since a positive result has a decisive clinical impact in the patient and familial context.

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The truncated somatostatin receptor sst5TMD4 stimulates the production of pro-angiogenic factors in *in vitro* and *in vivo* breast cancer models

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The presence of the truncated somatostatin receptor sst5TMD4 has been correlated with poor prognosis in breast cancer tumorsand its overexpression in breast cancer derived cell lines is associated with increased cell malignancy. The objective of this study was to examine the cellular and molecular mechanisms underlying this association in order to identify new molecular targets for diagnosis, prognosis or therapy of these tumors. Accordingly, in this study, a breast cancer derived cell line (MCF7) stably transfected with the truncated receptor sst5TMD4 and its respective control (empty pCDNA3 plasmid) were used to perform a gene expressionarray to determine changes in the expression pattern induced by the presence of the sst5TMD4 receptor. This approach revealed the existence of a profound alteration in the expression of genes involved in several tumoral processes such as cell survival or angiogenesis. Interestingly, subsequent studies by qRT-PCR in the same cell lines showed that key components of the angiogenic process, including VEGF system, were also clearly overexpressed in sst5TMD4-overexpressed cells. These data were confirmed in a xenograft model of *in vivo* tumoral growth, where inoculation of MCF-7 cells transfected with sst5TMD4 induced higher levels of VEGF, at both RNA (qRT-PCR) and protein (western blot and immunocytochemistry), than xenografts inoculated with mock cells. Altogether, these data demonstrate that the presence of sst5TMD4 induces an overexpression of certain pro-angiogenic factors such as VEGF in the breast cancer cell line MCF7, and in a xenograft tumoral model derived from that cell line. Therefore, these results support the role of sst5TMD4 in tumor malignancy observed in breast cancer and may help in identifying new lines of actions for future drug therapies for these tumors.

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The effects of cAMP in different neuroendocrine tumorous cells: the role of Epac and PKA in cell proliferation and cell adhesion

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cAMP is an ubiquitous second messenger that is implicated in the regulation of a wide variety of cell functions, including cell proliferation that is differently affected depending on the cell type. Although the effects exerted by cAMP were initially attributed to PKA activation, two exchange proteins directly activated by cAMP (Epac1/2) have been identified as cAMP targets able to mediate several cAMP effects. Aim of this study was to investigate the effect of cAMP on neuroendocrine tumor cells proliferation and to identify PKA and Epac differential involvement.

The activation of cAMP pathway by forskolin induced a significant increase in

BrDU incorporation and cyclin D1 expression in both cultured human gastroenteropancreatic-NET cells and QGP1 cell line. Conversely, cAMP increase by forskolin induced cell proliferation inhibition in carcinoid cell line H727 (33±4%, $P<0.05$ vs basal).
The divergent cAMP effects were mimicked by Epac and PKA analogs which activated Rap1 and CREB respectively. In particular, in QGP1 cells, both Epac- and PKA-selective analogs induced a similar stimulatory effect on cell proliferation (36±6 and 37±5%, respectively; *P*: NS). Similarly, in H727 cells a comparable inhibitory effects on cell proliferation was observed after both Epac and PKA selective activation (35±10 and 30±3% inhibition, *P*: NS).
Finally, Epac and PKA activators induced an increase of cell adhesion in QGP1 cells (48±8 and 32±5%,respectively; $P<0.05$ vs basal), this stimulatory effect being mediated by Epac analog only in H727 cells (63±12%, $P<0.05$ vs basal).
Our study indicates that cAMP induces positive or negative effects on neuroendocrine cell line proliferation, depending on the cell type, and that both Epac and PKA participate by activating different and partially unidentified signaling pathways. The previously unrecognized role of Epac as a mediator of cAMP effects in neuroendocrine cells open the way for the identification of molecular mechanisms underlying the pathogenesis of neuroendocrine tumors and may represent the basis for new therapeutic targets.

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Molecular mechanisms of unexpected promoting effects of progesterone and mifepristone on granulosa cell tumorigenesis

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Antiprogestine mifepristone (MF) has been shown to inhibit ovarian epithelial cancer (OEC) cell growth *in vitro* and *in vivo*. Recent clinical trials with MF for human OEC were unsuccessful, for unknown reasons. Progesterone (P_4) is believed to have preventive measures towards breast, endometrial or hOEC cancers. Hereby we analyzed the effects of P_4 and MF on ovarian granulosa cell tumorigenesis (GCT) *in vitro* and *in vivo*, and characterized their progesterone receptors (PGR): nuclear PGA and PGRB, membrane (mPRα, mPRβ, mPRγ) and membrane components PGRMC1 and PGRMC2. A supra-physiological dose of P_4 and MF, up to 5 μM, unexpectedly significantly stimulated cell proliferation in murine (KK-1 and NT-1) and human (KGN) GCT cell lines compared to non-stimulated group. Similarly, 1-month treatments of P_4 and MF *in vivo* (vs non treated tumor/control) also stimulated granulosa cell tumor progression in GCT transgenic mice expressing Simian Virus 40 T antigen under inhibin-α promoter (Inhα/Tag). The Inhα/Tag mice, harboring GCT by 5-month of age with 100% penetrance, expressed all PGR types. Non-treated Inhα/Tag GCT showed high cellular atypia, multinuclear and bizzare cells, cysts surrounded by connective tissues with hyperplastic and tumorigenic cell populations. P_4 and MF increased the Ki67 positive cells to 80-90 vs 60% in non-treated group. MF or P_4 treatments upregulated TGFβ1, TGFβRI, TGFβRII, TGFβRIII and SMAD3 expression of the GCTs. TGFβRII was non-detectable in control non-treated group ovaries indicating an impaired/disrupted anti-cancer action of TGFβ in the Inhα/Tag GCTs. Taken together, our results suggest that MF or P_4 treatments may induce TGFβRII in Inhα/Tag GCT and probably switch TGFβ function from tumor suppressive to pro-tumorigenic. In Inhα/Tag GCT, MF may act as selective PGR modulator agonist and be involved in tumor GCT progression by TGFβ1, TGFβRI, TGFβRII and SMAD3 pathway activation.

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BRAF V600E mutation in washing liquid of thyroid fine-needle aspiration: a surprising tool in cytological benign nodules

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Objective
Thyroid fine-needle aspiration (FNA) cytology is indeterminate in 15–25% of cases. Recently, cytological analysis was combined to molecular analysis to improve diagnostic accuracy. In the present study, washing liquid of FNA (wFNA) samples were tested for the BRAF V600E mutation, using high resolution melting (HRM) technology. The aim of this study was to demonstrate whether BRAF mutation analysis is accurate in wFNA and, when combined with cytological analysis and ultrasonography (US), can serve as an additional diagnostic tool.
Methods
Study design: cohort study involving 481 patients, corresponding to 648 FNA samples. All samples were subjected to both cytological and molecular analysis on the same aspiration: the former was conducted on cells smeared on a glass slide, the latter was carried out on fluids obtained washing the FNA needle with 2 ml of saline. BRAF V600E mutation analysis was performed by HRM after careful methodological validation for application to wFNA (sensitivity: 5%).
Results
The cytological results of the 648 FNA were: 136 (21%) 'non diagnostic' (Thy 1); 415 (64%) 'negative for malignant cells' (Thy 2); 80 (12.4%) 'inconclusive/in-determinate' (Thy 3); 9 (1.4%) 'suspicious for malignancy' (Thy 4); 8 (1.2%) 'diagnostic for malignancy' (Thy 5). The BRAF V600E mutation was found in 2 (2.5%) Thy 3, 6 (66.6%) Thy 4 and 6 (75%) Thy 5. Surprisingly, 5 (1.2%) Thy 2 samples resulted BRAF mutated. BRAF V600E mutations were confirmed by pyrosequencing in scraped Thy 2 cytological samples. Patients underwent thyroidectomy and the diagnosis of papillary carcinoma was confirmed at histology.
Conclusions
This study demonstrates that BRAF assessment can be accurately performed on wFNA and improves the diagnostic performance, regardless of cytological results. In perspective, stand-by wFNA samples could be analyzed 'a posteriori' in case of indeterminate cytology and/or suspicious US findings.

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Classic ductal sonographic criteria vs real-time elastography criteria in diagnosing nodular breast lesions

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Objectives
We evaluated the diagnostic power of different used evaluation criteria in ultrasound 2B, Doppler and elastography.
Method
Retrospective data analyses of all cases with breast lumps, that were evaluated and also operated during the study follow-up period. Study period: January 2011–April 2013 (Table 1).
Ductal breast ultrasound, Doppler and real-time elastography was performed with a HITACHI EUB 7500 HV machine, with 6–13 MHz variable frequency linear probe, with water bag, Hitachi Medical System, Tokyo, Japan. Ueno score and also strain ratio were measured for all described lesions. ACR4 lesions were referred to the surgeon. Some ACR3 lesions were also referred to the surgical cure. Extemporaneous and postsurgical histopathological exam was performed in all cases. Some ACR3 lesions were also referred to the surgeons because of cosmetic, pre-pregnancy, need of hormonal contraception use reasons.

Results
Study group was comprised only by the operated cases. We calculated the diagnostic power of different parameters in identifyiung cases with breast cancer.
Conclusion
There is a net diagnostic value difference in favor of real-time elastography, in identifying breast cancer cases.

Table 1

Parameter	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Lump size >2.5 mm	20.83	89.21	57.69	61.58
Perpendicular dominant axis	52.77	89.21	77.55	72.8
Iregular margins	48.61	89.21	76.08	71.09
Inhomogenous content	15.27	85.29	58.78	89.86
Spiculated shape	25.49	75.0	62.25	77.15
Increased vascularity	54.16	75.49	60.93	70.0
Three out of five criteria	63.81	63.75	68.64	58.62
Four out of five criteria	65.71	68.28	65.40	58.62
Five out of six criteria	68.42	50.74	61.17	58.62
UENO SCORE >3	90.41	81.91	79.51	91.66
FLR ratio >4.99	94.4	94.11	92.0	96.0

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P521

A case of insulinoma localized in pancreas tail that cannot be monitored with endosonography and abdominal MR but with contrast abdominal BT

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Introduction
Insulinoma is a rare neuroendocrine tumor. 90% of insulinoma is solitaire and benign, and 10% is malignant. Although seen at any age, it is most commonly noticed in 4th and 6th decades.
Case
A 78-year-old man was referred to a neurology clinic upon a sudden faint, disability to remember and meaningless behavior, and diagnosed with epilepsy in 2008. In 2012, he had a hypoglycemia attack (blood glucose 30 mg/dl) and was referred to Ege University. After consultation, he was hospitalized in order to investigate hypoglycemia etiology. His general status was moderate with BP: 140/80 mmHg and pulse: 78 b.p.m. Other system examinations were normal. His laboratory findings: FBG, 5 mg/dl; HbA1c, 4.9%; cr, 0.71 mg/dl; AST, 18 U/l; and ALT, 9U/l. Dextroz was continued as BG was below 20 mg/dl. The measurements at the time of hypoglycemia: insulin, 17.2 mlU/ml; C-peptide, 2.35 ng/ml; insulin:glucose ratio, 0.66; ACTH, 93.6; cortisol, 21.61 μg/dl; and HGH, 5.23 ng/ml. The clinical and laboratory results suggested insulinoma.

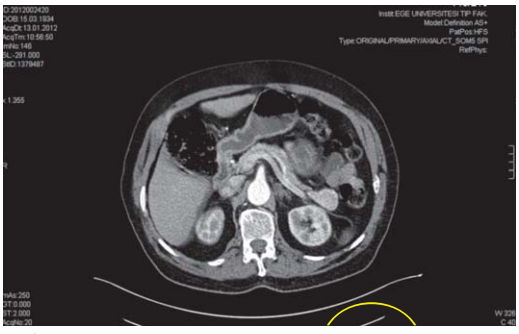

Figure 1

The endosonography showed age-related atrophy. His abdominal MR was normal.
In contrast abdominal BT, we found a 3.6×2.3 cm mass lesion associated with neuroendocrine tumor, localized in pancreas tail (Figure 1).
Arterial phase contrast BT
Hypophysis–adrenal axis was normal and PTH: 77.8; therefore, we didn't suggest MEN.
The patient had a pancreas distal resection.
Pathology report: neuroendocrine tumor well differentiated (Grade I), chromogranin A positive, and cytokeratin 19 positive.
Discussion
Insulinoma is an uncommon pancreatic β cell neoplasm with an incidence of 1/1 000 000. The most frequent symptom is neuroglycopenia, so patients are usually misdiagnosed and referred to psychiatry or neurology clinics. Although endosonography and MR are sensitive methods, they failed to localize insulinoma in our patient because of its place in the tail part of the pancreas. Multiphasic helical BT can detect 2/3 of insulinomas. Here, we aimed to highlight the importance of preoperative insulinoma localization.

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Adrenocortical carcinoma: a review of four cases

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Background
Adrenal carcinoma is rare endocrine cancer. Survival time is short and primary treatment is surgery.
Methods
Four patients with histopathologically diagnosed as adrenal carcinoma between 2007 and 2013 were evaluated retrospectively.
Results
Two of the patients were female and others were male. Their ages were 39, 50, 55 and 61 respectively. All the patients were admitted to the hospital with abdominal pain. Tumor diameters of the cases were 20, 18, 5 and 11 cm respectively. Tumor was on left side in three patients and on the right side in one patient. Three patients had active hormone secreting tumors that was cortisol. One patient had hormone-inactive tumor. Two patients were stage 4, one patient was stage 2 and one patient was stage 1 according to TNM classification. Two patients were treated with mitotane. Three of the patients died 5, 14 and 15 months after the operation respectively. One patient (39 years old, stage 2) is alive for 4.5 years after the operation.
Conclusion
Adrenal carcinomas have bad prognosis. The patients have been diagnosed at late stages. The most important survival criteria is complete surgical resection. The age of the patient at diagnosis might be an another survival factor. Mitotane treatment might be used in selected patients.

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P523

A rare case of an androgen-producing stromal luteoma of the ovary in a postmenopausal woman, diagnosed by means of selective venous blood sampling

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Background
Multiple diagnostic modalities may be needed to establish the source of excessive androgen production in women. The detection of testosterone-producing ovarian tumors by imaging techniques can be difficult because of their in same cases small size and radiological structure.

Case report
We describe a 55-year-old postmenopausal woman presenting with progressive severe virilization (Ferriman Gallwey-Score: 23–26), increased hair growth, male pattern baldness and deepening of the voice. Measurements of circulating hormones demonstrated severe hyperandrogenism with a markedly elevated total testosterone concentration of 775 ng/dl (reference 2.9–40.8 ng/dl) and elevated levels of androstendione and suppressed gonadotropines. Cortisol levels went down, but total testosterone inhibition did not occur after suppression test with dexamethasone. In addition, red blood count, hemoglobin and hematocrit values were elevated. An extensive pre-operative diagnostic work up was performed, including transvaginal ultrasound, abdomen–thorax computed tomography, abdomen–pelvic magnetic resonance imaging, as well endoscopic ultrasound, but all failed to localize an androgen-secreting tumor. Therefore, a selective venous catheterization and hormonal sampling (SVCHS) of the ovarian und adrenal veins were performed. The total testosterone concentration was significantly higher in the samples taken from the right ovarian vein (>1500 ng/ml; right:left ratio 2.8; and reference <1.44). An exploratory laparoscopic right saplingo-oophrectomy was performed and gave evidence of a right ovarian tumor. Immunohistochemical examinations revealed a stromal luteoma of the ovary. The patient's postoperative testosterone levels declined rapidly to normal levels.
Conclusion
Bilateral selective venous sampling from ovarial and adrenal veins can be valuable for the localization of small androgen-producing tumors and enable an operative cure, especially when imaging offers confounding results.

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P524

Fnab and calcitonin wash-out during exenatide therapy

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Aim
Medullary thyroid cancer (MTC) is 4.73 times higher among glucagon-like peptide-1 (GLP-1) agonist users. GLP-1 agonists are witheld in case of MTC or MEN. Serum calcitonin (Ct) does not increase to diagnostic level in small and nonmetastatic MTC. We report cytology and Ct wash-out results of fine-needle aspiration biopsy of thyroid nodules (FNAB) in type 2 diabetic patients receiving exenatide.
Methods
Eleven male and 66 female patients (31–76 years old) receiving exenatide therapy (5 μg bid for the 1st month and 10 μg bid afterwards) for type 2 DM were evaluated. Serum Ct and Ct wash-out of FNAB were measured using chemiluminescence immunoassay.
Findings
Of 45 patients with basal US evaluation, 19 had micronodules (43%) and 14 had nodules (33%) over 1 cm in size. One patient without baseline value, had Ct level of 482 pg/ml at the 5th month of therapy. She had multinodular goiter on US. Since basal Ct level and FNAB were absent, the relation between high Ct level and exenatide therapy could not be established. The other patients had normal Ct values both at baseline ($n=43$, 2.26 ± 0.66 pg/ml) and during follow-up ($n=65$, 2.28 ± 0.62 pg/ml). Three patients developed micro PTC. None of FNAB and histologic evaluation of papillary thyroid cancer (PTC) samples revealed C-cell hyperplasia (CHH). Ct wash-out levels of 21 patients were normal (2.47 ± 1.21 pg/ml).
Conclusion
Effect of GLP-1 analogue on thyroid tissue is still obscure. Normal serum and wash-out Ct levels and FNAB findings suggest exenatide is safe. Because of the index case it may be prudent to do basal US and FNAB as needed at least before therapy. Case it may be prudent to do basal US and FNAB as needed at least before therapy. Levels and FNAB findings suggest exenatide is safe. Because of the index case it may be prudent to do basal US and FNAB as needed at least before therapy and clinical meaning of it is obscure.
Conclusion
Normal serum and wash-out Ct levels and FNAB findings suggest exenatide is safe. Because of the index case it may be prudent to do basal US and FNAB as needed at least before therapy of FNAB and histologic evaluation of PTC samples revealed CHH. Sample of Ct wash-out levels were normal.
Discussion
PTC, MTC, CHH, and normal thyroid tissue bear variable GLP-1 receptors. Whether Ct level will rise along with CHH during GLP-1 analogue therapy and clinical meaning of it is obscure.
Conclusion
Normal serum and wash-out Ct levels and FNAB findings suggest exenatide is safe. Because of the index case it may be prudent to do basal US and FNAB as needed at least before therapy and rule-out any unknown MTC.

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P525

The presence of B-RAF V600E and K601E mutations in our Ligurian population

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Introduction
Differentiated thyroid carcinoma (DTC) is the most common endocrine neoplasm and its rate it's constantly increasing. Papillary thyroid carcinoma (PTC) represents 87% of all DTC and its incidence is raising at 89%. The thyroid carcinoma preoperative diagnosis consists in fine-needle ago aspiration (FNAB). However in the diagnostic cytology there actually is a 'grey zone', the 'follicular lesion of indeterminate significant or suspicious for follicular neoplasm' (Thy3 and Thy4 by British Thyroid Association). By date molecular analysis is coming a powerful diagnostic tool. The most common mutation found in PTC is B-RAF V600E detected in 50% of all PTC at the definitive histological diagnosis. There are, then, other mutations in the B-RAF as the K601E that *in vitro* demonstrates an oncogenic activity lower than V600E: the V600E kinase activity has a 2.5 times greater than the K601E that has been identified in follicular adenomas and, more rarely, in follicular carcinomas.
Purpose
The study purpose was to evaluate, in our Ligurian population, the effectiveness of surgery not only with the cytological diagnosis but also with the investigation of molecular genetics.
Materials and methods
patients (14 males and 41 females, average age 53 years) were evaluated between January and November 2013 with indeterminate cytological diagnosis. The FNAB material was fixed with cytofix on glass slides from which one was used for molecular diagnostics.
Results
The presence of B-RAF mutations was similar in Thy3 and Thy4 lesions (41% of Thy3 and 35% of Thy4). A B-RAF mutation was detected in 38% of all cases, 8% of these patients were males and 92% females. In 85% of cases, the mutation identified was the B-RAF V600E and in 15% of cases the B-RAF K601E. Of the cases in which a B-RAF mutation was detected, 15% were benign at the definitive histology, 85% of cases showed DTC (82% PTC and 18% follicular variant PTC) and no follicular neoplasm was detected. All B-RAF mutated cases with benignant histology were B-RAF K601E ones. Of those cases without B-RAF mutations which were carcinomas on definitive histology 45% were follicular carcinomas, 11% medullar carcinomas, 22% follicular variant PTC, 11% PTC and 11% trabecular neoplasm. Only considering classical variant PTC in 91% of cases there were correspondence between cytological diagnosis and definitive histology (in 9% of cases there were not B-RAF mutation neither at cytology neither at histology).
Conclusions
The presence of the B-RAF V600E mutation in our population suggests that a more aggressive surgical approach should be undertaken, a conviction that has already been expressed in the literature. The B-RAF V-600E mutation is present in the cytological material only in those patients with final histological diagnosis of PTC. However, in our limited number of cases, no correlation emerged between indices of malignancy and the B-RAF K601E mutation. In the course, it is a retrospective study to determine if patients carriers B-RAF V600E mutation have a worse outcome compared with WT ones.

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P526

The use of demeclocyclin in the syndrome of paraneoplastic inappropriated secretion of anti-diuretic hormone: about one observation

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Introduction
Hyponatraemia constitutes the most common hydro-electrolytic abnormality and the determination of its cause is important for patient's treatment, which can include the use of a pharmacological agent.

Observation
A 78-year-old woman suffering from a lung adenocarcinoma presents a chronic hyponatraemia ranging from 114 to 123 mmol/l, which cannot be corrected by fluid limitation alone. Clinical and biological assessment leads to diagnose a syndrome of paraneoplastic inappropriated secretion of antidiuretic hormone (SIADH). The tumor cannot be surgically removed, as metastases are present. A treatment with demeclocylin 600 mg daily is initiated, with a response within 6 days as natraemia increases to 137 mmol/l, with persistant efficacy at 2 months, and with good tolerance.
Discussion
In the face of a SIADH, the clinician can use few therapeutic strategies like aetiological treatment and fluid limitation. Demecloclycin can be highly efficient, probably due to a cyclic AMP pathway inhibition. Another family of drugs, vaptans or V2 ADH-receptors antagonists show interesting results in case of euvolemic or hypervolemic hyponatraemias.
Conclusion
The use of demeclocyclin has been very helpful for this lady suffering from an advanced stage lung adenocarcinoma, and who cannot benefit from an aetiological treatment, which is usually associated with correction of hyponatraemia. The precise mechanism of the drug is however not well understood yet, and deserves to be elucidated in pharmacological studies.

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P527

Could non-functional adrenal incidentaloma be a risk factor for atherosclerosis and metabolic disturbances?

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Introduction
Non-functional adrenal incidentalomas (AI) are currently quite important since they can also cause metabolic disturbances. This study was designed to evaluate possible insulin resistance indicators and cardiovascular risk factors in patients with non-functional AI.
Patients and methods
83 patients with non-functional AI were enrolled to the study. Control group consisted of 56 patients without any adrenal lesion. Fasting blood glucose, and insulin levels, lipid profiles, uric acid, homocysteine, fibrinogen, C-reactive protein (CRP) and adinopectin levels of study and control groups were determined. HOMA-IR scores and carotid intima media thicknesses (CIMT) of were determined as well.
Results
Fasting blood glucose (FBG), fasting insulin levels and HOMA–IR scores were found to be significantly higher in patients compared to controls ($P<0.001$ for all comparisons). Besides, total cholesterol and LDL-cholesterol levels, homocysteine and fibrinogen levels were found to be higher in patients group as well. No significant differences were found between patients and control groups in terms of adinopectin and uric acid. CIMT values were also found to be significantly higher in patients with AI than the controls (0.74 ± 0.14 vs 0.53 ± 0.09, $P<0.001$).
Conclusion
Patients with non-functional adrenal incidentaloma may be linked with insulin resistance, thus metabolic disturbances. Patients with AI are prone to have premature cardiovascular disease since their CIMT values are higher compared with controls.

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P528

Retrospective evaluation of adrenal incidentalomas in a tertiary care institution

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Introduction
We retrospectively evaluated all patients with adrenal tumours treated in our Department from 1.1.1999 to 1.10.2013.
Patients and methods
189 patients (110 females: 79 males, mean age of 57.5 years) were treated because of adrenal tumours. All patients underwent hormonal analysis and testing in order to check for hormonal activity. Tumours were classified according to gender, age at diagnosis, tumour localisation and size, as well as benignity and malignancy when postinterventional histopathological examination was conducted.
Results
133 patients had non-hormone secreting tumours (non-functional incidentalomas; 70.4%), 18 pheochromocytoma (9.5%), 13 Conn-syndrome (6.9%), 12 adrenal Cushing's disease (6.3%), one AGS and two sexual hormone-secreting tumours. Ten tumours could not be classified due to unclear test-results (5.3%). Cushing's disease was present in 11 females and 1 male. 164 (87%) tumours were unilateral there of 96 (50.8%) on the left and 68 (36%) on the right and 25 (13.2%) patients had bilateral tumours. Tumour size <3 cm occurred in 120 (63.5%), 3–6 cm in 54 (28.6%) and >6 cm in 15 (7.9%) of the cases. 61 (32%) patients were operated, thereof 88.8% of the cases with hormone-active tumours, and 8 (4%) were evaluated with ultrasound-guided biopsy. Malignancy was diagnosed in ten individuals (5.3%; three non-functional tumours, three pheochromocytomas, two Cushing's patients and two sexual-hormone secreting tumours) and benignity was confirmed in 56 (30%) patients. two surgical specimens with histopathological diagnosis of pheochromocytoma were suspicious of malignant alterations, one biopsy was not diagnostic.
Conclusions
Adrenal incidentaloma prevalence is rising due to widely available imaging devices. The majority is benign, of small size (<3 cm) and hormonally inactive. Adrenalectomy presents as the therapeutic method of choice in confirmed hormone-secreting tumours.

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P529

A rare ovarian carcinoma

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We present a rare association of ovarian carcinoid and virilization. A 65-year-old woman presented with a 9 years history of obesity, hypertension, dyslipidemia, stable angina, evaluated ambulatory for a postmenopausal virilization syndrome and flushes, with high testosterone and 17-hydroxyprogesterone (17OHP) levels without suppression during the 2×2 mg DXM test, normal gynecological evaluations with no tumor formation involving uterus, ovaries and adrenals at the pelvic ultrasound imaging and abdominal CT scan performed during the first referral.
The physical examination showed an obese patient with seborrhea and hirsutism. Blood analyses pointed to hyperuricemia, hypercholesterolemia, normal HbA1c and glycaemia, diabetes at OGTT, elevated estradiol and testosterone with CA125 in the normal range. Pelvic examination, ultrasound and CT showed a tumor developed in the left adnexal area tube and left ovary, left adrenal hyperplasia. Plasmatic and free urinary cortisol, ACTH were normal without responsiveness to the 1 mg DXM overnight test, normal DHEAS, 17OHP increased basal with lack of responsive to stimulation.
Our patient was referred to the Oncology Institute for a total hysterectomy with bilateral adnexectomy. Postoperatively, she returned with the diagnosis of insular ovarian carcinoid, confirmed at immunohistochemistry. After surgery, seborrhea and hirsutism improved. Blood analyses pointed to basal cortisol and ACTH in the normal range, positive response to 1 mg DXM overnight; serotonin, cromogranin A, neuron specific enolase and 5HIA, urinary MN and NMN in the normal range, 17OHP, total and free testosterone normalized with 17-KS slightly increased.
The CT scan screening did not find any secondary determination. In conclusion this case is peculiar due to a very rare association (only six published cases until now), flushes being present in the absence of secondary determination and the changed response of cortisol to DXM 1 mg test.

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P530

Impotentia coeundi as the presenting symptom of a pheochromocytoma

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A 37-year-old Caucasian male, with a history of worsening erectile dysfunction, presented to the emergency department for night onset of severe headache and projectile vomiting, complaining of pain in the left hypochondrium, radiating to the ipsilateral lumbar region. The patient was on therapy with tadalafil 5 mg one tablet once a day and ciprofloxacin 500 mg one tablet twice a day for 1 week, on indication of his urologist. The patient reported to suffer from headaches for about 1 year and worsening impotentia coeundi. Objectively, it was detectable orthopnea, tachypnea, sinus tachycardia with a heart rate of 170/m', blood pressure 250/150 mmHg, oxygen saturation of haemoglobin: 90%,diffuse rales on chest auscultation. After treatment with furosemide, diltiazem, urapidil hydrochloride and oxygen, the patient was subjected to computed tomography of skull –brain, chest and abdomen with and without iodinated contrast, echocardiogram, blood tests. The key findings were: small subcortical left parietal bleeding, multiple pulmonary ground-glass consolidations, and a solid round mass (diameters 113×114 mm), well-defined, containing inhomogeneous density areas (necrotic-hemorrhagic pattern), with post-contrast ehancement effect, in close relationship with the tail of the pancreas and the left kidney. The echocardiogram showed left ventricular eccentric hypertrophy (diastolic diameter 57 mm) and good contractile function (left ventricular ejection fraction: 64%). As a collateral finding, the brain vascular system was highlighted even in the absence of iodinated contrast. The patient was subsequently stabilized with α-blockers, adequately rehydrated and underwent surgery in state of good hemodynamic balance. The dosage catecholamines and metanephrines provided very high values. Histology confirmed the diagnosis of pheochromocytoma.
The current patient condition is that of *restitutio ad integrum*.
The following are the main features of this clinical case:
i) impotentia coeundi is not normally listed among the classic or more frequent symptoms,
ii) the coincident daily intake of tadalafil could have a possible triggering effect on crisis,
iii) the high degree hyperadrenergic-induced haemoconcentration provided an unusual contrast-like effect in the vascular brain system.

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P531

Clinical management of insulinomas: a single institution's experience

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Background
Although very rare, insulinomas are the most commonly occurring endocrine tumor of the pancreas. The aim of this study was to review the clinical presentation, diagnostic approach and management of patients with an insulinoma.
Methods
22 insulinoma patients, with an age range of 20–79, were included and evaluated according to their clinical presentation, blood biochemistry, imaging studies, operative management, pathological manifestations, postoperative and follow-up outcomes.
Results
The majority of the patients were female (65.2%) with a mean age of 53.0±18.8 years at the time of diagnosis. Their routinely measured mean morning fasting blood glucose levels were 72.4±18.3 mg/dl and only six patients had low blood glucose levels < 60 mg/dl. Their fasting blood insulin level and C-peptide levels were all in normal ranges. All the patients were admitted to the medical center and underwent 72 h supervised fast. Diagnosis of insulinoma was determined in 22 patients (female/male = 14/8) by hyperinsuliemia during hypoglycemic episode and was assured in 21 patients with histological investigation after operation. A pancreatic mass was observed on transabdominal ultrasonography (US) or computerized tomography (CT) in 18 of the 22 (81.8%) patients preoperatively. Enucleation was performed in 17 patients (81.0%) if the lesion is clearly localized and small. Distal pancreatic resection was needed in the rest of four patients. Postoperative complications such as postoperative cyst and intra-abdominal infection were observed in six patients.
Conclusion
A high serum insulin level during hypoglycemic episode is highly specific for diagnosing insulinoma and US and CT appears to be a substantially useful preoperative investigation procedure for localizing a pancreatic adenoma. In unexperienced hands, intraoperative ultrasonography is not highly conclusive procedure for pancreatic tumor localization.

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P532

Comparison of chromogranin A levels in serum and plasma (EDTA2K) and the respective reference ranges in healthy males

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Introduction
Chromogranin A (CgA) is a main, nonspecific marker of neuroendocrine tumours (NET). There are various commercially assays for the measurement of CgA concentration in serum or plasma. These assays differ in analytical techniques (RIA, ELISA, CLIA), have different standardization, and use different antibodies which recognize different epitopes of CgA molecule.
Aim of study
Our study was designed to confirm the noted earlier differences in CgA levels measured in serum and plasma, and to establish respective references ranges in a group of healthy males.
Material and methods
145 male blood donors (age mean±s.d. 35.7±9.4; range 19–61 years). At each collection, blood was withdrawn into two tubes: one in EDTA2K (plasma) and one with clot activator (serum). Chromogranin A was measured by immunoradiometric kit (CIS bio, France).
Results
In blood donors, the median (and the range) of CgA concentration determined in serum samples was 42.0 ng/ml (16–108 ng/ml) and in plasma samples was 58.0 ng/ml (23–153 ng/ml). The differences between serum and plasma ranged 15–79% (median 26%). Plasma CgA levels were significantly higher in relation to serum CgA levels ($P<0.0001$). Correlation of CgA in serum and plasma was $r=0.9099$; $r^2=0.8493$; $P<0.01$. The determined reference ranges for CgA measured in serum and plasma in males were: 21.0–108.0 and 31.0–153.0 ng/ml respectively.
Conclusions
Significant differences in the concentrations of CgA measured in plasma and in serum demand application of separate reference ranges adjusted to the sort of the investigated material.

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P533

High JAG1 expression in adrenocortical carcinomas is associated with better prognosis

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Background
Adrenocortical tumors consist of benign adenomas (ACA) and highly malignant carcinomas (ACC). Dysregulation of the Notch signalling pathway is implicated in several cancers with oncogenic or tumor suppressor functions. JAG1 is a Notch1 ligand of the Jagged family and a common target gene for Notch and Wnt/β catenin pathways. It has been reported that upregulated expression of JAG1 enhances cell proliferation in ACC.
Material and methods
The mRNA expression of NOTCH1, JAG1, and some specific target genes (HES1, HES5, and HEY2) was evaluated in 49 fresh frozen samples (13 normal adrenal glands, 17 ACA and 19 ACC) by quantitative real-time PCR.

Immunohistochemistry was performed in 202 tissues on paraffin slides (six normal adrenal glands, 25 ACA, 171 ACC) for the evaluation of JAG1 protein expression.
Results
The mRNA expression of NOTCH1, HES1 and HES5 was similar in the three groups. On the other hand, HEY2 and JAG levels were higher in ACC than in ACA (both $P<0.005$). The JAG1 protein was expressed (H-score from 1 to 3) in significantly more ACC than ACA (73 vs 39%, $P<0.005$). Interestingly, high JAG1 protein expression was also associated with a better prognosis in ACC patients. This was true both in terms of overall survival ($n=126$, median 110 vs 30 months, HR = 1.9, 95% CI = 1.2–3.1, $P=0.0068$) and disease-free survival ($n=45$, median 49 vs 18 months, HR = 2.0, 95% CI = 0.9–4.2, $P=0.07$).
Conclusion
Notch1 signaling pathway activation might be involved in adrenocortical tumor progression and need to be further investigated. However, high JAG1 expression seems to play rather a protective role in established ACC and its expression might represent a new positive prognostic factor.

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P534

Role of metformin on recurrence-free survival in neuroendocrine tumors

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Introduction
Recent data suggest that metformin has antineoplastic properties in different type of cancer. Effects of metformin have never been investigated in neuroendocrine tumors (NET).
We aim to determine the role of metformine on recurrence-free survival (RFS) in NET patients.
Materials and methods
A retrospective analysis was conducted comparing NET patients with recent diagnosis (<3 year) of diabetes mellitus (with HbA1c $\leq$ 7%), treated with metformin (group A) to not diabetic NET patients without metformin (group B) with comparable clinical and pathological characteristics. RFS was evaluated by Kaplan–Meier analysis.
Results
We analysed data from 12 patients in group A (five F, seven M; mean age 62 years, follow-up since diagnosis: 4–173 months) and 24 patients in group B (13 F, 11 M; mean age 57 years, follow-up: 6–149 m). G1 and G2 NET were five and seven in group A, 12 and 12 each in group B. Primary NET was in bronchi (one in group A, two in group B), gastrointestinal tract (four in group A, eight in group B), pancreas (seven in group A, 14 in group B). Five patients in group A and seven in group B had liver metastases at diagnosis. Recurrence rate was lower in group A than in group B (8 vs 42%). Median RFS was not reached in group A, it was 86 months in group B (95% CI:19–153, $P<0.05$). There were no statistically significant differences in RFS between the two groups according to grading, metastases, NET therapies, other anti-diabetic drugs in association with metformine.
Conclusion
In diabetic NET patients, metformin therapy seems to be associated with improved RFS. Prospective studies are needed to better define the anti-neoplastic role of metformin in NET.

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P535

Expression of inhibitor of apoptosis protein BIRC7/livin in adrenocortical tumors

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Introduction
Adrenocortical tumors consist in frequent benign adenomas (ACA) and rare highly malignant carcinomas (ACC). BIRC7/livin gene, a member of the inhibitors of apoptosis family, plays an important role in tumorigenesis in a variety of malignancies. Different studies demonstrated that BIRC7 over-expression represent a risk factor for cancer development and progression. The aim of our study was to evaluate the expression of BIRC7 in normal adrenals and adrenocortical tumors.
Methods
BIRC7 mRNA expression was detected by quantitative real-time RT-PCR analysis in fresh-frozen tissue samples (24 ACC, 18 ACA, and 17 normal adrenal). The correlation between BIRC7 levels and several clinical parameters was also investigated.
Result
BIRC7 mRNA expression was similar between adenomas and normal adrenals. However it was significantly increased in malignant adrenocortical tumors ($P<0.005$ vs both ACA and normal adrenal). No significant difference was found between cortisol-secreting and non cortisol-secreting tumors. In the ACC group, we did not observe any significant correlation between BIRC7 levels and clinical risk factors, such as age, tumor size, Weiss score, ENSAT tumor stage, Ki67-index and number of metastasis at diagnosis.
Conclusion
To our knowledge, this is the first study that investigates the BIRC7/livin expression in normal adrenal and adrenocortical tumors. We demonstrate that BIRC7 is specifically over-expressed in ACC. As previously reported for different tumor types, these findings open a new prospective for the use of BIRC7 as a potential therapeutic target in ACC.

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P536

Aurora kinases inhibitors Vx-680, SNS314 and ZM447439 in adrenocortical tumors

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Background
Adrenocortical tumors (ACT) include benign and malignant forms. Adrenocortical carcinomas (ACC) are highly malignant neoplasms with poor prognosis and strong metastatic potential. Aurora kinase family members (AK) are serine/threonine kinase involved in the regulation of mitosis. Aurora kinase A (AKA) promotes centrosome maturation and spindle assembly, while aurora kinase B (AKB) is necessary for spindle assembly checkpoint and cytokinesis.
Aim
To evaluate AK inhibitors, Vx-680, SNS314 and ZM447439 in adrenocortical cell lines (SW13 and H295R cells).
Materials and methods
Diverse biomolecular assays were performed on SW13 and H295R cells using AK inhibitors at different times and concentrations. Moreover AK expression was evaluated in 67 ACT by qRT-PCR. The cohort of patients was subdivided into 22 ACC, 14 aldosterone producing adenoma, 17 cortisol producing adenomas, six non-secreting adenomas and eight normal adrenal tissues.
Results
AK inhibitors significantly reduced SW13 cell viability at 72 h. Cell cycle distribution and clonogenic assay results were modulated by AK inhibitors in SW13 cells, as well as[^{3}H] thymidine assay. Furthermore Vx-680 at 200 nM induced an evident decrease of AKA and AKB in SW13 cells analyzed by western blot. No appreciable change was perceived in H295R cells. Direct sequencing of AKA and AKB provided no substantial difference between SW13 and H295R cells. AK are also expressed in all tissues and indeed ACC samples overexpressed AKA (91%) and AKB (87%).
Conclusions
Our results demonstrated that AK inhibitors seem to strictly act on SW13 cells, suggesting their potential use on some malignant tumors, as SW13 cells are considered a metastatic depot in adrenal cortex. On the contrary H295R cells showed drugs resistance, which may not be imputable to genetic background. Further analysis are needed to elucidate this distinctive behavior of H295R cells.

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P537

Sunitinib induced hypocalcaemia during treatment of pancreatic neuroendocrine tumours

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Background
Although sunitinib, an oral multitargeted tyrosine kinase inhibitor of RET, VEGFR, PDGFR, c-KIT used for cancer treatment, has a reported prevalence of hypocalcemia of 35%, this has not been documented in pancreatic neuroendocrine tumour (pNETs).
Methods
We present three, out of 12, patients with pNETs treated with sunitinib who developed grade 1, 2 and 4 hypocalcemia according Common Terminology Criteria for Adverse Events v3.0 (CTCAE) criteria.
Results
A 51-year-old man with a stage IV, grade 1 pNET developed disease progression besides treatment with somatostatin analogues (SA). Nine months after sunitinib was initiated he developed symptomatic grade 2 hypocalcemia (7.2 mg/dl) necessitating treatment discontinuation and calcium supplementation. A 53-year-old man with MEN-1 with stage IV, grade 1 pNET was treated with Whipple's operation and SA. Following disease progression he was initially treated with everolimus that was discontinued due to severe anemia and treatment with sunitinib was initiated. Nine months later he developed grade 1 hypocalcemia (8.2 mg/dl) that improved with dose reduction. A 58-year-old man with a long history of a stage IV, grade 2 pNET had received various treatments including chemotherapy, interferon, peptide receptor radionuclide therapy (PRRT) and SA. During the course of his disease he developed severe and refractory hypercalcemia due to PTHrP secretion by the tumour. Following disease progression he was treated with sunitinib and 1-month later he developed grade 4 hypocalcemia ($<$6 mg/dl). Following reinstitution of treatment his previous refractory hypercalcemia became easily controlled.
Conclusion
Hypocalcemia induced by sunitinib during treatment of pNET can occur relatively common with wide severity that may necessitate treatment modification. However, this potential side-effect may be of therapeutic significance in patients with refractory hypercalcemia.

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P538

Cyclin D1 levels are involved in the resistance to m-TOR inhibitors in human bronchial carcinoids

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Background
Bronchial carcinoids (BC) are still orphan of medical therapy. We previously demonstrated that the typical BC human cell line NCI-H727 is sensitive to Everolimus, in terms of cell viability reduction, while the atypical human BC cell line NCI-H720 is not. However, the mechanisms underlying this phenomenon have not been fully clarified.
Aim
The aim of our study is to investigate the mechanisms of resistance to mTOR inhibitors in BC cells.
Methods
Cell cycle protein profiling was performed throughout G0/G1/S phases evaluating important complexes regulated during these transition phases at different cell-cycle times, such as CDK2/Cyclin E, CDK4/CyclinD1 and p27Kip1.
Results
The two human BC cell lines, NCI-720 and NCI-727 cells, showed different levels of cell cycle-regulating proteins during cycle progression. We found that under starvation the resistant cell line (NCI-720 cells) still expressed most of the cell cycle regulating protein, while in the sensitive cell line (NCI-727 cells), proteins as p27, cyclin D1 and E were highly down regulated. In addition we observed that, during cell cycle progression, CyclinE/CDK2 complex seems to be more expressed in resistant NCI-H720 cells as compared to NCI-727 cells. In contrast, CyckinD1/CDK4 is more expressed in the sensitive NCI-H727 cell line, while p27 does not show a different expression pattern during cell cycle progression in the two cell lines.
Conclusion
The pattern of proteins involved in cell cycle regulation is clearly different in the two cell lines, suggesting a possible involvement of these molecules in the mechanism of mTOR inhibitors resistance.

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P539

Follicular lesion of undetermined significance in thyroid nodules fine needle aspiration cytology: a revision of 95 cases

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Introduction
The 'Atypia of Undetermined Significance/Follicular lesion of Undetermined Significance' (AUS/FLUS) category of the Bethesda Classification for thyroid nodules fine needle aspiration cytology (FNAC) is reserved for specimens that contain cells with architectural and/or nuclear atypia that is not sufficient to be classified as suspicious or malignant. Our objective is to report our experience in the follow-up and outcome of patients with AUS/FLUS in thyroid nodules FNAC.
Methods
From 1529 patients with 1838 thyroid nodules, 11.4% of the nodules was diagnosed as AUS/FLUS. From 111 patients with FLUS, we analyzed 95, 88 females and seven males.
Results
26 patients (27.4%) had directly undergone to neck surgery and five (19.2%) had malignant nodules. 51 patients (53.7%) repeated FNAC. On the second FNAC, 17 (33.3%) nodules were benign, 22 (43.1%) were AUS/FLUS, 11 (21.6%) were non-diagnostic and 1 (1.9%) was malignant. From the patients who were submitted to a second FNAC, 12 undergone to surgery and two nodules were malignant. 18 patients (18.9%) kept clinical follow up without repeating FNAC or surgery. Six patients (6.3%) repeated FNAC a third time: four nodules were benign and two non-diagnostic.
Among the 95 patients with FLUS, 38 (40%) were submitted to neck surgery and seven had a malignant diagnosis. The malignancy rate in the 95 patients with AUS/FLUS was 7.4%, but 18.4% in the patients who did surgery. The malignancy rate was 16.7% in patients who repeated FNAC and 19.2% in patients who undergone directly to surgery.
Conclusion
In this category the recommendation is to repeat the FNAC rather than excision. We suggest the follow-up of these patients should be individualized and discussed in multidisciplinary teams. The combination of clinical suspicion, ultrasound characteristics and BRAF mutation testing could help in this decision.

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P540

Monitoring of pheochromocytomas development in proto-oncogene RET mutation's carriers

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Proto-oncogene RET encodes a receptor tyrosine kinase. Germline point mutations of RET result in development of multiple endocrine neoplasia, type 2 (MEN 2). MEN 2 phenotype is correlated with intragene localization of germline mutation. The disease has three main subtypes, MEN 2A, MEN 2B and FMTC. Each of subtypes is associated with high risk of medullary thyroid cancer, MEN 2A and MEN 2B with 50% risk of pheochromocytoma, MEN 2A with 15–30% risk of primary hyperparathyroidism. Pheochromocytomas in MEN 2 patients are usually localized in adrenal glands, being benign, and often bilateral. The aim of this study was to evaluate the development of pheochromocytomas in patients with germline proto-oncogene RET mutations. Among 228 gene carriers, most often MEN 2 was caused by mutation in codon 634 (36.85%). Pheochromocytoma was diagnosed in 36 patients, in 24 with mutation in codon 634, in six in codon 918 and in three in codon 620, in two in codon 618 and in one in codon 611. The youngest age at pheochromocytoma onset was 15 years, this was in patient with mutation in codon 918. In 6 (16.7%) gene carriers the pheochreomocytoma was the first manifestation of MEN 2. Most of patients in

time of pheochromocytoma diagnosis didn't present classical symptoms. Pheochromocytomas were detected with use of adrenal imaging (TK, MR, MIBG scintigraphy) and determination of urinary metoxycatecholamines. In 11 (30.5%) tumor was bilateral, initially with mean size of 3.6 cm.
This study demonstrates necessity of regular follow-up in germline proto-oncogene RET mutation carriers using additional exams, not only clinical evaluation. Taking in to account different interferences influencing biochemical assessment, we suggest that adrenal imaging (TK/MR) should be used as complementary follow-up method. The start of regular monitoring depends on the age of the known youngest patient with diagnosed pheochromocytoma.

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P541

Efficiency of ultrasound-guided percutaneous thyroid nodule biopsy among patients hospitalized in the department of internal medicine

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Introduction
Fine needle aspiration of thyroid nodules is the most frequently performed ambulatory and recommendations for its performance are quite accurately described in the national and international guidelines. However, there is always a need to analyze the effectiveness of such proceedings.
The aim of this study was to analyze such effectiveness in group of hospitalized patients.
Method
The reason for hospitalization in the vast majority are not thyroid disease, and indications for ultrasound of the thyroid, as well as indications for biopsy, as well as pathological evaluation, determine the guidelines of national endocrine society.
Results
We perform a biopsy of the thyroid in about 20–25% of hospitalized patients (from 476 to 693). From 2 to 5% of biopsies required consultation with the national center of oncology and/or were qualified for surgical removal of the change. Thyroid cancer was confirmed in up to two patients per year ($<0.3\%$). We do not have any information on the subsequent detection of thyroid cancer assessed changes in our department as mild. The estimated cost of the detection of one thyroid cancer was $\sim$ 10 000 Euros.
Commentary
Our method have sufficient sensitivity, the cost of one cancer diagnosis was relatively high, however much cheaper than other methods of screening tests. The incidence of thyroid cancer in our region is likely to be significantly lower than in other parts of Europe. So perhaps the experts should develop regionally differentiated recommendations of diagnosis of thyroid nodules.
Conclusion
Performing a biopsy of the thyroid according to the recommendations has a very high sensitivity, but in regions with low incidence of thyroid cancer cost of such a diagnosis is quite high.

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P542

Multiple endocrine neoplasia type 1 and 2: a retrospective study

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Introduction
Multiple endocrine neoplasia (MEN) are rare including MEN1:association of pituitary, pancreatic and parathyroid tumors and MEN 2 regrouping NEM2a: medullary thyroid cancer (MTC), pheochromocytoma and parathyroid tumor and NEM2b with ganglioneuromas. They're caused by autosomal dominant mutation: MEN1 gene (MEN 1) and RET protooncogen (MEN 2).
Aim
Report the phenotypic and evolutionary characteristics of MEN.
Population and methodology
28 patients with MEN were hospitalized from 1981 to 2013. All patients received a guided exploration and molecular study for NEM 2.
Results
A preponderance of MEN2 (n:20) is observed. In the eight MEN1's cases, median age = 41 years, first manifestation was pituitaty adenoma in 50%, following by hyperparathyroidism 37.5% and one case of cervical mass. Five of them seem have a sporadic form and three have familial antecedent of MEN1.The association hyperparathyroidism + pituitary adenoma was observed in 75% of the cases associated to: pancreatic (12.5%),adrenal tumor (25%), digestive carcinoid (12.5%), paraganglioma (25%).The pituitary adenoma was equally a prolactinoma (33.33%) or a non functional pituitary adenoma, a somatotrop (16.66%) and a gonadotrop adenoma (16.66%).Hyperparathyroidism was constant, caused by a unique adenoma (25%) or hyperplasia (12.5%),management of the others' in progress. In 20 MEN2 cases, we note three sporadic ones and 17 organised in three families, median age was 35.35, first manifestation: MTC (60%), phéochromocytoma (40%).The phenotype was complete in 35%, partial in 65% with a correlation genotype–phenotype in four families that express 634 mutation of RET gene. The circumstances of discovery was a cervical mass in 20%, high blood pressure 35% and a clinical screening 45%. We note a remission after management in only 35.7% of MEN1 patients and 40% of MEN2's.
Conclusion
MEN 1 and 2 are rare. We observed a preponderance of the MEN2. The molecular genetic testing should be extended to all of the MEN families to facilitate the management of these patients in a multidisciplinary approach.

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P543

The prevalence of malignancy in thyroid incidentalomas in an iodine-replete area

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Background
Thyroid incidentalomas are reported with increasing incidence in the last decades. The rate of malignancy in these nodules may reach 9% or higher, depending on the patients selection.
Material and methods
A retrospective study was done on 429 patients with nodular goiter (issued from an iodine-replete area), admitted in the Clinic of Endocrinology, Timisoara, Romania, from January 2011 to December 2013.
Results
The prevalence of thyroid incidentaloma was 22.3% (96 cases). The incidentalomas were diagnosed in most cases on thyroid ultrasound (74%), carotid duplex scanning (13.5%), computed tomography (7.3%) and magnetic resonance imaging (5.2%). The rate of malignancy was 2.08% in incidentaloma group (two cases with follicular variant of papillary thyroid carcinoma (FVPTC)). Among the 49 non-incidentalomas operated patients, the rate of malignancy was 26.5% (four papillary thyroid cancers, four FVPTCs, one anaplastic cancer, one follicular cancer, one Hürtle cell carcinoma, one mixed PTC: classic and FVPTC, one malignant non-Hodgkin lymphoma). There were no significant differences regarding: age, gender, number of nodules, thyroid functionality, or ultrasonographical features between incidentalomas and non-incidentalomas. The 'suspicious' nodules at ultrasound were evaluated by fine-needle aspiration biopsy (FNAB). FNAB, performed in 22 incidentalomas, showed: three follicular lesions, three indeterminate, four non-diagnostic, the remaining being benign smears. In the non-incidentaloma group, FNAB (performed in 57 cases) showed: 11 follicular lesions, nine indeterminate, five non-diagnostic, two papillary thyroid cancers, the remaining being benign smears. Among the operated cases, thyroid cancer was diagnosed in 25.4% (15/59), representing 3.5% of the total nodules. The rate of malignancy was 33.3% (3/9) in nodules with <10 mm diameter respectively 24% (12/50) in nodules larger than 10 mm.
Conclusion
Thyroid incidentalomas should be assessed as non-incidenalomas (ultrasonography, cytological examination), because of the similar rate of malignancy.

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P544

A major Endocrine Unit's experience: the combined role of ultrasound scans and fine needle aspiration in the management of thyroid nodules

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Introduction
The first-line investigation of thyroid nodules is ultrasonography. Since the introduction of fine needle aspiration cytology (FNAC) in the last 2 decades, the diagnostic accuracy of thyroid malignancy has massively improved. This study aims to examine the sensitivities of ultrasonography and FNAC respectively, evaluating our centre's practice.
Methods
Retrospective data were collected from ultrasound scan and FNAC reports of patients who were histologically proved to have thyroid malignancy after thyroidectomy between the period of January 2010 and October 2013 in a major regional endocrine unit in the UK. Ultrasound scan results were categorised into benign, indeterminate and suspicious of malignancy; while FNAC results had five categories including non-diagnostic (Thy1), non-neoplastic (Thy2), follicular (Thy3), suspicious (Thy4) and diagnostic (Thy5). Sensitivities were determined.
Results
100 patients were histologically diagnosed with thyroid malignancy. 81 patients had both ultrasound scan and FNAC reported. The sensitivity of ultrasonography was 39% (positive if suspicious of malignancy) and that of FNAC was 59% (positive if Thy3, 4 or 5). Of the positive scan results for thyroid malignancy, 66.6% also had a positive FNAC. The average number of months between ultrasound appointment and first thyroidectomy was 2.8.
Conclusions
The combined sensitivity of ultrasonography and FNAC is statistically higher than that of each test on its own in diagnosing thyroid malignancy. Most patients have both tests done especially if there is diagnostic ambiguity on their clinical presentations. Based on the results of this study and recent literatures, FNAC should be readily available at ultrasound appointment to avoid the delay of any surgical management. This study warrants the use of one-stop clinic providing ultrasound-guided FNAC that would not only enhance the diagnostic accuracy but also provide more efficient care for patients presenting with thyroid nodules. Further research is required to investigate the cost-effectiveness of a one-stop clinic.

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P545

Ultrasonography as a first-line investigation of thyroid nodule: is it still the case? An audit to examine and reflect on our practice in a regional endocrine unit

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Introduction
Ultrasonography is safe, fast and radiation-free. This audit, based on the American Thyroid Association (ATA) Management Guidelines (revised in 2009), aims to establish if our regional unit meets the recommended standards of using ultrasonography to aid the management of thyroid malignancy and to make further suggestions to improve practice.
Methodology
Retrospective data were collected from ultrasound scan reports of patients who had thyroid malignancy in an endocrine unit in the UK. Inclusion criteria: scans between January 2010 and October 2013; histological diagnosis of malignancy. Ultrasound scan results were reported as benign, indeterminate and suspicious of malignancy by experienced ultrasonographers. ATA recommends, 'thyroid ultrasounography should be performed in all patients with known or suspected thyroid nodules'.
Results
Out of the 100 patients who had a histological diagnosis of thyroid malignancy, 23% was reported to have benign nodules, 32% indeterminate, 39% suspicious of malignancy, 4% not have scans reported and 2% not have scans performed. It is unclear why some ultrasound results were not reported. The two cases that did not have an ultrasound scan done presented with massive thyroid nodules with significant tracheal deviation.
Outcomes
Although only 94% of patients with thyroid nodules had ultrasound scans, one may suspect that the two cases without scan might not have been put through unnecessary investigations due to their clinical presentations highly suggesting a malignancy. A protocol should be established to ensure all scan results were reported to facilitate future references in the management of thyroid malignancy. Moreover, this audit also prompts the revalidation of ultrasonography as a first-line investigation. With the increasing reliability of fine needle aspiration (FNA) in the diagnosis of thyroid nodules, ultrasound scan might not add much extra information to the management. Follow-up study is needed to examine the isolated and combined benefits of ultrasound scan and FNA.

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P546

Pheochromocytoma and neurofibromatosis type 1: description of case

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Introduction
The pheochromocytomas are rare neuroendocrine tumors that can occur sporadically or, in about 30% of cases, in the context of family syndromes. Ten percent are malignant. Neurofibromatosis type 1 is an autosomal dominant disease that is associated with the occurrence of these tumors. Pheochromocytoma appears at 0.1– 5.7% of patients with neurofibromatosis type 1, and are usually solitary and benign lesions.
Clinical case
A 50-year-old female, with history of neurofibromatosis type 1, hypertension, depressive syndrome, divergent strabismus and smoker. Medicated with irbesartan 300 mg, sertraline and alprazolam.
She was referenced to our service of Endocrinology due to a 6 cm nodular lesion in the right adrenal, detected in renal CT.
On physical examination, the patient presented high blood pressure, cafe-au-lait spots and cutaneous neurofibromas. The adrenal functional study revealed high levels of plasma metanephrines, vanillylmandelic acid, urinary fractionated catecholamines and metanephrines. The MRI showed a massive heterogeneous right adrenal gland mass with $48 \times 48 \times 63$ mm, with hyperintense signal on T2-weighted, internal cystic areas and areas of hyperintensity on T1-weighted that may correspond to areas of hemorrhage. The mass presents frank capture of contrast and marked restriction in diffusion weighting. This findings favour the diagnosis of pheochromocytoma. The I131-MIBG showed an image compatible with right adrenal pheochromocytoma. After appropriate preoperative therapy, laparoscopic right adrenalectomy was performed. Patological examination revealed a pheochromocytoma with invasion of capsule and adjacent adipose tissue, without vascular invasion. After surgery, levels of plasma metanephrines, vanillylmandelic acid, urinary fractionated catecholamines and metanephrines normalized. Currently, she has good blood pressure control without medication.
Conclusions
We consider important to present this case due to the rarity of the case, the possibility of malignancy, a hypothesis strengthened by tumor size, and the challenge of long-term follow-up of these tumors.

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P547

Ganglioneuroma of the adrenal gland: a case report

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Introduction
The adrenal ganglioneuroma are rare, benign and well differentiated tumors that arise from neural crest tissue. Most patients with adrenal ganglioneuroma are asymptomatic, and most of these are non-secreting tumors. They are usually found incidentally on abdominal imaging study for another reason.
Case
A 53-year-old female, with a history of hypertension diagnosed at age 30, dyslipidaemia, depressive disorder and hysterectomy for uterine prolapse. Medicated with spironolactone, potassium, atorvastatin, omeprazole, fluoxetine and lorazepam. History of repeat hospitalizations in the Internal Medicine Service for recurrent hypokalaemia.
During the investigation of hypertension and hypokalaemia, a hypodense nodule in the left adrenal gland was detected on abdominal CT. She was referred to our service of Endocrinology due to suspected primary aldosteronism.

She presented with asthenia, anorexia, cramps and muscle aches with a few months of evolution. Physical examination demonstrated no significant finding. Adrenal CT showed a left adrenal with hypodense nodule with 3 cm. Abdominal-pelvic MRI revealed a left adrenal with complex cystic mass with thick walls, where it identifies a mural nodule with 11×7 mm, questioning the possibility of tumor or pseudocyst cystic degeneration, and of considering their surgical excision. Endocrine tests were normal.
Left adrenalectomy was performed by laparoscopy. The histological diagnosis was adrenal ganglioneuroma.
Nephrology consultation for investigation of hypokalemia excluded renal interstitial disease with potassium loss. Currently, she attends Psychiatric consultation on suspicion Munchausen syndrome.
Conclusion
We present this case due to the rarity of the clinical entity and the clinical presentation, which initially pointed us to another diagnosis. Ganglioneuromas are generally non-secreting tumors, and most patients are asymptomatic at diagnosis, as in the case presented. The prognosis of patients who underwent complete tumor resection is excellent.

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P548

Efficacy and safety of transarterial chemoembolization of unresectable neuroendocrine liver metastases

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Background
Trans-catheter arterial chemoembolization (TACE) is a method of treatment of unresectable liver metastases from neuroendocrine tumours (NETs) which is effective in the control of symptoms and tumour growth.
Aim
To evaluate clinical outcome: radiologic, biologic, symptomatic response and safety of TACE procedure.
Method
31 patients underwent 140 TACE procedures during 2003–2011. Tumour responses were measured by CT and MRI, and were assessed using the RECIST criteria.
Results
NETs originated from pancreas ($n=5$), small bowel ($n=11$), colon ($n=1$), lung ($n=5$), unknown primary localization ($n=9$). According to WHO/ENETs criteria, majority were NETs G1–G2. Almost all patients had received other medical treatment. Tumour response: none of the 31 patients had complete response. After third TACE a partial response was observed in two patients, stable disease in eight patients, and there was none of the patient with progressive disease. After the third TACE partial response was observed in three, stable disease in five and progressive disease in four patients. Biologic response: increased values of CgA were found in 82% patients. There was statistically significant correlation between radiological response and plasma CgA levels ($r=0.517$, $P=0.008$). Symptomatic response: all patients reported symptom improvement (diarrhoea, flushing) after first TACE. Carcinoid syndrome was less controlled after third TACE (83%). The correlation between radiological response and urinary 5HIAA level also existed, but it was not statistically significant. Safety: all patients experienced some form of postembolization syndrome. Serious adverse events were noted after 12 TACE (8.6%) in six patients, without treatment-related deaths. Severe complications were kidney failure associated with tumour lysis syndrome and DIK in two patients and carcinoid crisis in four patients.
Conclusion
TACE is effective and safe treatment for patients with hepatic metastases from NETs. The goals of treatment include radiologic response or disease stabilization, symptom and biochemical control, and improvement in quality of life.

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P549

Efficacy of lanreotide autogel in men1-related gastrinomas: a case series

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GEP NETs, especially gastrinomas, occur in 40–70% of MEN1 patients and represent the main cause of death in these patients.
We aim to investigate the efficacy of lanreotide autogel (ATG) in the treatment of MEN1-related gastrinomas.
We report a monocentric series of seven MEN1 patients (three M, and four F) treated with lanreotide ATG (120 mg/4 weeks) for a mean period of 62.1 months. Plasma gastrin levels have been measured at diagnosis, 3 months after starting lanreotide and then every 6 months. Five of the seven patients underwent surgery, at least 3 months after starting lanreotide treatment, while two patients refused surgical treatment.
Mean plasma gastrin levels at diagnosis were 5562 pg/ml (1300–17 178 pg/ml; n.v. 30–115) and fell, after 3 months of treatment, to 117.1 pg/ml (53–241 pg/ml; mean reduction 78.9%). Five patients underwent surgery and three of these had persistent hypergastrinemia. In these patients, the treatment with lanreotide was resumed with normalization of gastrin plasma levels and disease stabilization. Two patients refused surgery: during follow-up gastrin levels remained controlled with no evidence of disease progression.
Lanreotide ATG proved efficacy in the biochemical control of hypergastrinemia with normalization of plasma gastrin levels in 70% of patients and a mean reduction of 78.9% after the first 3 months of treatment. Moreover, lanreotide demonstrated efficacy in the long-term control of disease and allowed tumor stabilization in all patients.

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P550

The effectiveness of yttrium90/lutetium177-labeled somatostatin analogues treatment in functional pNETs

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Introduction
Therapy with somatostatin analouges is usually ineffective to remove hormonal symptoms in patients with functional pancreatic neuroendocrine tumors (pNET). Alternative treatment modalities, to control symptoms of excessive hormonal production, are necessary. Thus, the aim of our study was to evaluate results of radiopeptide treatment in patient with functional pNET.
Materials and methods
92 patients with pNET (49 women and 43 men, median age 58) have been observed for the last 10 years (2004–2014). Functional pNET were diagnosed in 21 (23%) of them, including 9 (10%) insulinomas 4 (4.5%) gastrinomas, 4 (4.5%), glucagonomas, 2 (2%) VIP-omas and 2 (2%) with mixed hormonal activity. Seven patients with inoperable functional pNET and high expression of somatostatin receptor (confirmed in scintigraphy) were treated with radiolabelled somatostatin analouges. In all of them other treatment modalities were ineffective to control clinical symptoms of hormonal production.
Results
Clinical symptoms, resulting from excessive hormonal production, decreased after the first course of radiopeptide therapy and completely resolved at the end of the treatment in all treated patients. Three subjects suffered from symptoms recurrence after a median time of 22 months. Clinical response was accompanied by tumor regression according to RECIST criteria in three patients.
Conclusions
Radiolabelled somatostatin analogues, administered in patients with pNET, allow for good control of clinical symptoms and objective tumor response.

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P551

Evaluation of vegf and endocan/esm-1 expression in pnets and correlation with Ki67 and prognosis

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Endocan has been reported as specific of endothelial tumor cells and was shown to be expressed by tip cells during angiogenesis process.
The principal aims of the study are the assessment of immunohistochemical VEGF and Endocan expression in functioning and non functioning pNETs and the comparison of these markers with clinical features, Ki67 and TNM staging.
We collected a total number of 79 pNETs surgical specimens for immunohistochemestry (IHC). The population chosen has been classified according to type of diagnosis, sex, age, grading and staging.
We report the preliminary results of IHC for VEGF and Endocan performed on 46 patients. The expression of Endocan is limited to endothelial cells within neoplastic tissue. VEGF is expressed in the cytoplasm of tumoral cells. VEGF and Endocan expression is strictly connected, considering that Endocan expression upon endothelial cells is stimulated by VEGF production by neoplastic cells (P <0,001). The grading is directly correlated to the stage and in our series this finding is confirmed (P 0.001). We correlated Endocan and VEGF expression to Ki67 and TNM classification. We found a significant correlation between Endocan and VEGF expression and metastatic disease (P 0.005 and <0.001 respectively).
These preliminary data seem to show that Endocan and VEGF immunohistochemical expression in pNETs may be predictive markers of aggressiveness.

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P552

Insulinoma, recurrent hypoglycaemia: a debilitating condition

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Insulinomas are rare neuroendocrine tumours that classically present with a combination of symptomatic hypoglycaemia, low serum glucose values and resolution of symptoms post glucose ingestion.
We describe a 65-year-old lady who repeatedly presented over several years with recurrent infections, predominantly of the urinary tract, nausea and diarrhoea, necessitating frequent hospital admissions. Despite extensive investigations, no clear cause for her symptoms was identified. These ongoing episodes were incidentally noted to occur with clinical and biochemical hypoglycaemia (serum glucose values even as low as 1.7 mmol/l), seen to correct by administering intravenous dextrose. She was subsequently, referred to her local Endocrinologist. 0900 h Cortisol and short synacthen test were normal. A 72 h fast was unfortunately terminated prematurely due to severe symptomatic hypoglycaemia (serum glucose of 2.8 mmol/l). A raised C-Peptide of 798 pmol/l and Insulin of 8.2 (3-17 μ/l) with a negative sulphonylurea screen, at the time of hypoglycaemia, biochemically confirmed inappropriate endogenous insulin secretion, as seen with insulinomas.
Magnetic resonance imaging could not exclude a small insulinoma. She declined all further investigations, hence Diazoxide was commenced and although the frequency of hypoglycaemia reduced markedly, her nausea worsened. Diazoxide was, therefore, replaced by twice daily injections of short-acting octreotide, which achieved glycaemic control and she reported some improvement of her nausea. It was then decided to trial Lanreotide, which has successfully controlled both her hypoglycaemia and nausea, consequently reducing hospital admissions and allowing our patient to regain a decent quality of life.
Diagnosis of insulinomas is usually dependent upon clinical presentation, confirmation of hyperinsulinism and diagnostic imaging. This was a difficult case where the clinical suspicion of insulinoma was confirmed following initiation of medication to suppress insulin release.
Although rare, it is paramount that insulinomas are considered in patients with unexplained hypoglycaemia.

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P553

Gastro-entero-pancreatic neuroendocrine tumors (GEPNETs) – 10 year experience of one center

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GEPNETs are rare tumors of very variable biology, particularly proliferative potential. Improved knowledge of the clinical course of disease may lead to proper identification of patients requiring more aggressive approach.
Aim
i) characteristics of GEP-NET patients of the Endocrinology Department, University Hospital in Krakow, Poland; ii) identification of factors influencing their 5-year survival.
Material and methods
Study included 122 patients of the Endocrinology Department (69 females, 53 males; mean age at diagnosis 57±15 years) living in Krakow or Krakow district, diagnosed with GEPNET between January 2002 and December 2011.The following factors were assessed: primary focus localization, grading (WHO), staging (AJCC/UICC), distant metastases at diagnosis, hormonal activity, and survival.
Results
The mean follow-up time was 4.9±2.8 years. The most frequent primary localization of GEPNET was small intestine (20%), followed by pancreas (19%), rectum (19%),stomach (17%), appendix (16%) and colon (9%). NET G1 accounted for 69%, NET G2 for 26%, NEC for 4%, MANEC for 1% of analyzed GEPNETs. NET G1 and G2 were included in staging analysis – 57% of patients were diagnosed at stage I. 77% of G1 tumors were diagnosed at stage I, majority of G2 GEPNETS at stage IV (58%), P<0.001.Distant metastases at diagnosis were found in 34% of patients. Disseminated disease was found in 78% of GEPNET originating from colon, 62% of pancreatic or small intestine GEPNETs, and in none of appendiceal GEPNETs (P<0.001). 90% of GEPNETs were non-functioning ones. The overall five year survival as 85%. In univariate analysis, higher stage according to AJCC/UICC, grade NET G2, metastases at diagnosis, were associated with poorer prognosis. In standardized multivariate models advanced stage and metastases were the independent risk factors of poor outcome.
Conclusions
Analysis of large groups of GEPNET patients followed up in one center allows the identification of factors influencing patients survival.

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P554

Epidemiology of gastro-entero-pancreatic neuroendocrine tumors in Krakow and Krakow district area

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Cancer registers are important tools in improving the knowledge of epidemiology of rare malignancies, such as gastro-entero-pancreatic neuroendocrine tumors.
Aim
To assess the epidemiology of GEPNETs in Krakow and Krakow district area between January 2007 and December 2011.
Material and methods
To assess the epidemiology of GEPNETs in Krakow area a register was created, based on independent sources of information. 88 patients (49 females and 39 males) aged 59±17 years diagnosed with GEPNETs were included in further analysis. 75% of them were followed in the Endocrinology Department, University Hospital in Krakow. The following parameters were assessed: primary tumor localization, grading (WHO), staging (AJCC/UICC), distant metastases at diagnosis, and standardized GEPNET incidence rate.

Results
The most frequent primary localization of GEPNETs was small intestine (20%), followed by appendix (18%), pancreas (16%), stomach (16%), rectum (15%). Well differentiated GEPNETs prevailed (NET G1 constituted 64% of the group, NET G2 28%, and NEC 8%). Most of the tumors (63%) were diagnosed at stage I according to AJCC/UICC. Distant metastases were found at diagnosis in 31% of patients (to regional lymph nodes in 25% and distant in 18% of patients). Metastases were most frequently observed in NETs of colon (67%), whereas none of the appendiceal NETs was disseminated at diagnosis. The standardized incidence rates of GEPNETs in Krakow and Krakow district area ranged from 1.5 to 2.7 cases/100 000 persons per year, an average of 2.1/100 000 persons per year. The highest incidence was noted in the oldest patients (4.8/100 000 persons per year in subjects aged 60 years and older). No statistically important trend in GEPNETs incidence between 2007 and 2011 was noted.
Conclusions
GEPNET incidence in Krakow and Krakow district area is similar to the incidence observed in most European countries. Cancer register was proved to be important tool in evaluation of GEPNET epidemiology.

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P555

Factors influencing survival of patients diagnosed with gastro-entero-pancreatic neuroendocrine tumors in Krakow and Krakow district area

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Abstract
Identification of factors influencing survival of the gastro-entero-pancreatic neuroendocrine tumors patients may improve their management by better selection of subjects requiring more closed follow-up and more aggressive therapeutic approach.
Aim
To assess factors influencing survival of GEPNET patients livingin Krakow and Krakow district area.
Material and methods
The data from GEPNETs register run in the Endocrinology Department, University Hospital in Krakow, were assessed. 88 patients (49 females and 39 males) aged 59 ± 17 years diagnosed with GEPNETs between January 2007 and December 2011, living in Krakow and Krakow district area,were included in further analysis. 75% of them were followed in the Endocrinology Department, University Hospital in Krakow. Factors influencing 2-year survival were assessed.
Results
The mean follow-up period was 2.7 ± 1.6 years. Two-year survival was 77%. In univariate analysis the following factors were associated with poor prognosis: grade NET G2 ($P < 0.001$), stage III (AJCC/UICC) ($P = 0.002$) or IV ($P < 0.001$) at diagnosis, both nodal and distant metastases at diagnosis ($P < 0.001$), colonic GEPNETs ($P = 0.039$), and management outside specialized GEPNET center ($P = 0.007$). In multivariate standardized models the independent risk factors of poorer prognosis were: higher stage at diagnosis (eight- to tenfold increased risk of death for stages III and IV vs I), metastases at diagnosis (tenfold increased risk of death), the residence outside the limits of Krakow city (three- to fivefold increased risk of death), and the management outside the Department of Endocrinology, University Hospital in Krakow (sevenfold increase in risk of death).
Conclusions
The GEPNET patient survival is influenced not only by the disease extend at diagnosis (staging) and by proliferation indices (grading), but also by area of residency (probably due to mismatch in health care providers availability) and the experience of the center taking care of GEPNET patients.

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P556

Catecholamin crisis as a first manifestation of multiple endocrine neoplasia type 2A

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Introduction
Multiple endocrine neoplasia type 2A (MEN2A) is a multi-glandular autosomal dominant genetic disorder which, most typically, includes medullary carcinoma of the thyroid, pheochromocytoma and primary hyperparathyroidism. The authors present a case study of a young man in whom cardiogenic shock was the first manifestation of pheochromocytoma and MEN2A.
Case report
A 30-year-old man without a past history of hypertension or any other chronic medical problems was admitted to the Emergency Department with severe abdominal pain, vomiting, fever and dyspnea. On admission, he had high blood pressure and tachycardia. Within a few hours cardiac and respiratory failure developed, followed by sudden cardiac arrest in the mechanism of asystole. Resuscitation was conducted effectively, yet the patient remained unconscious, demanding intubation and mechanical ventilation for a few days. The clinical picture of catecholamine crisis (high temperature, high labile values of blood pressure, supraventricular arrythmias, cardiomyopthy) was relevant to the image studies – the computer tomography revealed bilateral adrenal tumors with typical radiologic features of pheochromocytoma (heterogeneous, regular masses with areas of necrosis and calcification). The hormonal tests confirmed the initial diagnosis of pheochromocytoma (elevated 24 h urine collection of metanephrine, elevated plasma metanephrine and chromogranin A). The patient underwent laparoscopic right adrenalectomy and classic left adrenalectomy. Histopathology revealed bilateral adrenal pheochromocytoma that stained positive for chromogranin and synaptophysin with Ki 67 index $< 2\%$. Further investigation of the patient showed medullary carcinoma of the thyroid and the patient was qualified for total thyroidectomy. The concomitance of the primary hyperparathyroidim was ruled out. The genetic screening for RET revealed mutations in exon 11, p C634R. The gene mutation was also detected in the patient's father and sister.
Conclusion
The presence of pheochromocytoma at young age raises the suspicion of the hereditary background of the disease and requires further investigation, especially towards MEN2A.

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Adrenal incidentaloma: is it a disease of elderly? A clinical study of 2650 cases registered at a single endocrinological center

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It is generally believed that frequency of incidentally found adrenal tumours (adrenal incidentaloma(AI)) increases with age. Our study aimed at an analysis of age patterns in our group of patients with AI.
Design
Material: 2650 patients, 1943 womens, 707 men. The diagnostic basis: clinical examination, imaging studies, hormonal determinations, pathomorphological and cytochemical investigations of the surgically removed 755 adrenal tumours. The material has been divided into three groups: i) probably benign tumours – 2363; ii) adrenal carcinoma – 192; iii) metastatic tumours – 62 patients, in three subsets – up to 30 years old, 30–60 and over 60 years of age. A group of 17 patients with other malignant tumours did not change the statistics.
Results
In the total population we found 107 patients up to 30 years old (4%), group 1 – 73 = 3%, group 2 – 33 = 17%, and group 3 – 0. Patients ranging 31 – 60 years of age: group 1 –1278 = 54%, group 2 – 113 = 59%, group 3 – 28 = 47%. The patients aged over 60 years: group 1 – 1012 = 43%, group 2 – 46 = 24%, group 3 – 33 = 53%.

Conclusions
i) Only in patients with metastatic tumours a prevalence of patients over 60 years of age was noted. ii) In the most numerous group, including benign tumours patients aged 31–60 years dominated iii) Interestingly, there were 4% of young patients, up to 30 years of age, in the total group of AI, the most frequently in the ACC group (17%), exceeding the data from the literature. iv) In the total group of 2650 cases, 31–60 years old patients dominated over other age compartments; thus adrenal incidentaloma is a disease of mainly middle-aged patients.

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Abstract unavailable.

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Evaluation of demographic data of patients with adrenal incidentalomas

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Background and aim
Adrenal incidentalomas are discovered incidentally. Incidence has been increasing proportionally to the use of radiographic imaging. We aimed to evaluate patients with adrenal incidentalomas demographically.
Subjects and methods
This study was performed between January 2010 and February 2013. Total 320 patients (55.4 ± 11.7 years) with adrenal incidentaloma (86 (26.8%) male (55.2 ± 11.6 years) and 234 (73.1%) female (56.2 ± 12.3 years) were included. All data were shown as mean ± s.d.. $\chi 2$ and Pearson's correlation mathods was used and values $P < 0.05$ as accepted statistical meaningful.
Results
Majority of cases was in 6th and 7th decades in both gender. First diagnostic procedure was ultrasound in 24.8%, MRI in 14.9% and CT in 60.2%. Cause of radiologic imaging was renal and liver disorders in 71.2%, thorax pathology in 20.4%. Location of incidentaloma of all patients was 48.4% in right side, 41.8% in left side and 9.68% bilateral. Whereas location of incidentaloma of male patients 53.4% in right side (*n*: 46), 34.8% in left side (*n*: 30) and 11.6% bilateral (*n*: 10). In female patients 46.5% in right side (*n*: 109), 44.4% in left side (104) and 13.2% bilateral (*n*: 31). Mean mass size of male patients (33.9 ± 22.9 mm) was higher than female patients (28.6 ± 20.0 mm) ($P = 0.002$). All cases were divided into three groups in according to tumor sizes < 40 mm, 40–60 mm and > 60 mm. In male patients number of mass size between 40–60 mm (*n*: 17, 19.5%) and > 60 mm (*n*: 8, 9.1%) was higher than female patients (respectively *n*: 18, 7.6% and *n*: 12, 5.1%). Mean mass size of < 40 age patients, was significantly larger than other (40–65 and > 65 years) patients ($P = 0.003$).
Conclusions
Adrenal incidentalomas has a clear female predominance. Most common diagnostic procedure of adrenal incidentaloma was CT. Main cause of radiologic imaging was renal and liver disorders. Mass size of male patients was higher than females.

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P560

Expression of FSH hormone receptors in pituitary adenomas: a marker of tumour aggressiveness?

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Background
In our earlier study we found that pituitary adenomas, like other human tumours, express ectopically follicle stimulating hormone receptors FSH in intratumoral blood vessels endothelia and/or tumoral cells. The aim of the present paper is to provide the more detailed data on FSHR expression in different subtypes of pituitary adenomas and to evaluate its possible role as a prognostic and/or predictive biomarker in these tumours.
Material and methods
Forty-two pituitary adenomas, surgically removed, were immunostained with antibodies against the pituitary hormones, antigen Ki–67 and 1–190 fragment of FSHR.
Results
The positive immunostaining was found in blood vessels endothelia of 88% of adenomas and in tumoral cells of 40% adenomas. In tumoral cells, the incidence of at least moderate FSHR immunostaining is significantly higher in invasive tumours (68%) in comparison with non-invasive (12%) ones and higher (Albeit not statistically significant) in invasive-proliferating adenomas (Ki67 > 3%, grade 2b) in comparison with invasive but non-proliferating (Ki67 < 3%, grade 2a) ones.
Conclusions
The present study confirms that pituitary adenomas ectopically express FSHR in intratumoral blood vessels endothelia and tumoral cells. Moreover, the expression in tumoral cells is prevalent in invasive and proliferating adenomas vs non-invasive and non-proliferating tumours.

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Malignacy prevalance and related conditions in adrenal incidetaloma

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Background and aim
Incidence of adrenal incidentaloma is increasing proportionally to the use of radiographic imaging and there were two questions that whether malignant or functional. We aimed to evaluate patients with adrenal incidentalomas in terms of malignancy.
Subjects and methods
This study was performed between 2010 and 2013. From 320 patients with adrenal incidentaloma, total 52 patients who underwent surgical intervetion were evaluated. Indications for surgery were tumor size > 4 cm and adrenal hyperfunction. All data were shown as mean ± s.d. χ^2 and Pearson's correlation methods were used and values $P < 0.05$ as accepted statistical meaningful.
Results
Of 320 patients 52 underwent (16.2%) to surgical intervention (19 non-functional adrenal incidentaloma > 4 cm), 15 subclinical Cushing's syndrome (SCS), and 18 pheochromocytoma). Malignancy was determined in only 12 of total 320 (3.75%). In remained 40 patients (76.9%), benign histopathology was determined (14 non-functional, 14 SCS and 12 pheochromocytoma. In the evaluation of cases with malignancy; total five malignacy were determined in non-functional patients (leiomyosarkom, liposarkom ve renal cell carcinoma, lymphoma and metastasis of small cell lung carcinoma). Malignancy was found in only one case (metastasis of renal cell carcinoma) in SCS patients and six in patients with pheochromocytoma. We evaluated all malignant cases in terms of tumor size and found that; there was a correlation between tumor size and malignancy. In patiens with tumor size ≤ 60 mm; malignancy were determined only two patients (2/29, 6.9%), whereas malignancy were found in ten patients (43.5%) in tumor size > 60 mm group. We could not determine any malignancy in pateints whose tumor size < 4 cm and 4–6 cm. There was no meaningful difference between gender and age of the patients.

Discussion
Malignancy incidence is low in adrenal incidantalomas and tumor size is important in the prediction of tumor behaviour.

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Consolidation treatment with somatoatatin analogues after radiopeptide therapy

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Background
Although neuroendocrine tumours (NET) constitute a very heterogeneous group, most of them express somatostatin receptors that enable treatment with somatostatin analogues(SA), which proved to be effective both as bio- or radiopeptide therapy. However, little is now about combining this two treatment modalities.The aim of our prospective study was to evaluate results of radiolabeled somatostatin analogues (PRRT) with or without long lasting 'cold' SA as consolidation treatment.
Materials and methods
Only patients without carcinoid syndrome were included into the study. All were treated with PRRT (four to five cycles repeated every 6–12 weeks). After the last cycle of PRRT treatment response was evaluated with scintigraphic, radiological and biochemical examination. Thereafter patients were randomly assigned either to treatment with SA or observation group. Initiation of next line of therapy was left to discretion of treating physician.
Patients were followed-up at 4–12 months intervals with radiological examinations (CT or MRI) and receptors scintigraphy. Median time to progression was measured from the start of PRRT treatment till the day of disease progression confirmed in radiological or scintigraphic examination.
Results
patients (79 in SA and 46 in observation group) were included into the study. Twenty-eight patients (57%) from observation group started SA treatment due to development of carcinoid syndrome.
After median follow-up of 34 months, 81 (65%) of patients progressed and 48 (38%) died. Median time to progression was 29 months. There was no difference between patients in SA and observation group. SA treatment after PRRT was well tolerated and no G3-4 side effects were observed.
Conclusions
Preliminary results suggest that consolidation treatment with SA did not improve results of PRRT. However, larger number of patients and longer follow-up is necessary.

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Analysis of ultrasonographic parameters influencing thyroid nodules elasticity

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Introduction
Elastography is a method of tissue stiffness assessment. It was already demonstrated that thyroid cancers are less elastic than benign lesions. However, little is known about other factors, which might influence the stiffness of thyroid nodules and disrupt the prediction of malignancy using this technique. The aim of this study was to conduct the first systematic assessment of factors potentially affecting elasticity of thyroid lesions.
Methods
122 patients with thyroid nodules admitted for thyroidectomy underwent preoperative ultrasonography and sonoelastography. The definite diagnosis of thyroid lesions was based on histological examination. First of all, the elasticity of cancers and benign lesions was compared. Secondly, an influence of composition, size, localization, nodularity and selected laboratory parameters on thyroid nodules elasticity was evaluated. Association between above mentioned factors and elasticity was assessed in benign lesions.
Results
There were 22 malignant and 371 benign lesions. There were significant difference in tissue stiffness between benign and malignant nodules (maximal stiffness 55.6 vs 174.2 kPa, $P<0.0001$). Analysis of benign lesions revealed that presence of some sonographic features is associated with decreased elasticity. Benign nodules with calcifications ($P<0.0001$) had significantly increased stiffness. Partially cystic nodules were significantly less elastic than solid ones ($P=0.03$). There was positive correlation between the nodule size and elasticity ($P<0.0001$). Lesions localized in the isthmus were significantly less elastic than nodules in other localizations ($P=0.0001$).
Conclusions
We identified several attributes of lesions, including the size and composition that influence the recorded stiffness values of the lesion and need to be considered during interpretation of the results. According to our study, the stiffness values are increased in case of nodules containing calcifications, cystic component, those of size above 20 mm and localized in isthmus.

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Differential TNFα and Toll-like-receptor 4-signaling in endocrine tumors after tumor- vascular- disrupting Agent ASA404 (Vadimezan) and TNFα treatment

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ASA404 (Vadimezan) belongs to a class of agents with disrupting properties against tumor vasculature. Herein, putative therapeutic applicability was investigated in preclinical models for neuroendocrine tumors of the gastro-enteropancreatic system (BON) and adrenocortical carcinoma (NCIh295). Upon treatment of tumor bearing mice we detected a significant disruption of microvessels, decrease in cell proliferation, increase of apoptotic cells and extensive necrosis in BON tumors while no comparable effects were detectable in those of NCIh295 origin. As TNFα-signaling had been proposed to mediate parts of ASA404 dependent effects we utilized these models based on their different responsiveness for characterization of TNFα synthesis and signaling *in vitro* and *in vivo*. While NCIh295 tumors showed higher basal TNF receptor 1 expression and a comparable increase in serum TNFα levels, a significant increase in intra-tumoral TNFα secretion as well as TNFα-specific activation of downstream NFκB and caspase 3/7 signalling was present mainly in the BON model. Furthermore, we detected high levels of Toll-like-receptor TLR4 and a significant increase in the expression of its adaptor protein MD-2 specifically in ASA404 treated BON tumors, while both was not detectable for NCIh295. As TNFα is an important downstream component of the TLR-network this could be an additional reason for intra-tumoral TNFα alterations. Moreover, we identified at RNA level several members of an inhibitory feedback loop downstream of both pathways, including TNFAIP3/A20, TNIP1 and NFKκBIA, as elevated at baseline in the adrenocortical carcinoma tumor model. Confirmation of this deregulation at protein level is ongoing and was so far succesful for TNFAIP3/A20 suggesting altogether basal inhibition of both pathways as one putative reason for the detected impairment in therapeutic response.

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Effect of thiazolidinediones: PPARγ agonists on hormones secretion by cells of human adrenocortical cancer *in vitro*

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Introduction
Adrenocortical carcinoma (ACC) is characterized by the high malignancy of the lesion, poor prognosis and high mortality rate. The surgical treatment and available chemotherapy have generally low efficacy so the search for new therapeutic options is still necessary. Some research indicated that thiazolidine-diones (TZDs)–synthetic ligands of peroxisome proliferator-activated receptor γ

(PPARγ) have oncostatic action on neoplasm, including endocrine tumours. Moreover, previous investigations (ours and others) have shown the inhibitory effect of TZDs on the growth of human adrenocortical cancer *in vitro* and *in vivo* conditions. Therefore, in the present study, we decided to examine whether TZDs influence the secretion of adrenocortical hormones.
Materials and methods
The experiment was conducted on human adrenocortical carcinoma line H295R, whose cells posses the ability to produce cortisol, aldosterone and adrenal androgens. The cancer cells were treated with two TZDs – rosiglitazone (ROS) or pioglitazone (PIO) at the concentrations 10^{-8}–10^{-5} M for 3 days. In the culture medium, we measured the levels of the following hormones: aldosterone, cortisol, DHEAS, androstendione and 17-hydroxyprogesterone by using chemi-luminescence immunoassay and RIA.
Results
Both TZDs at most of the concentrations have increased DHEAs level. Besides, PIO stimulated cortisol secretion by cancer cells at all tested concentrations and ROS increased the hormone level only at the highest concentration. However, TZDs did not change significantly the levels of other adrenal hormones.
Conclusion
Agonists of PPARγ, despite the inhibitory effect on the growth of adrenocortical carcinoma, do not reduce the hormonal activity of cancer cells. So, it can be presumed that oncostatic action of TZDs and their influence on the synthesis of adrenal hormones are unrelated and depend on a different intracellular mechanism.

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P566

Primary neuroendocrine carcinoma of renal: a rare case report

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We report a case of local recurrence and multiple lymph node and pulmonary metastases of renal carcinoid 1 year after nephrectomy in a 61-year-old woman. Primary renal carcinoid tumor arising from renal parenchyma or renal pelvis is a rare neoplasm. The patient was incidentally found to have a mass lesion in the left kidney and left nephrectomy was performed. Histological examination including immunohistochemical for chromogranin A and synaptophysin studies confirmed the diagnosis of the atypical primary renal carcinoid. Tumor in the present case report was not associated with any other renal diseases. Renal carcinoid is mostly detected incidentally by imaging, and is rarely accompanied by symptoms such as flank pain, hematuria or a palpable mass. During follow-up computed tomography demonstrated a local recurrence and multiple lymph node around the inferior vena cava and pulmonary metastases. After scintigraphy of whole body octreotide theraphy was started. After few months the patient started peptide receptor radionuclide therapy somatostatin analogs labeled with ^{90}Y in neuroendocrine tumors (NETs). The administered activity of ^{90}Y-DOTATATE to the patient was based on 7.4 GBq/m2 body surface area in three cycles, with amino acid infusion for nephroprotection.In presented patient we did not get stabilization of disease and in the middle of the 2013 year she died. Combinations of octreotide with other targeted therapies may improve patient outcomes. Renal carcinoid tumor is a rare neoplasm, early recogniction of disease may help in increasing time to progression.

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P567

Neuroendocrine carcinomas of the thymus: two case reports

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The neuroendocrine tumor of thymus (TNET) is an extremely rare disease. It can occur sporadically or as a part of the multiple endocrine neoplasia (MEN1) syndrome. TNET may secret hormons (ectopic ACTH production). It is a potentially malignant tumor which often develops distant metastases. Its prognostic factors are the tumor size, histological grade, Ki67 index, paraneoplastic symptoms, surgical resection and Masaoka staging. The options for treatment are radical surgery, chemotherapy (temozolomide, platinum based agents) and somatostatin analogue therapy (SSA).
First case: investigations of a 38-year-old male patient revealed the presence of primary hyperparathyroidism due to a parathyroid adenoma, a pituitary adenoma, a pancreatic neuroendocrine tumor, neuroendocrine cancer of the thymus, hormonally inactive adrenocortical adenomas, and a non-endocrine tumor (facial angiofibroma). All these components together witnessed for the diagnosis of MEN 1. Parathyroid and thymic tumors were surgically removed. The patient has been kept under continuous SSA therapy for his pancreatic and thymic tumors. The clinical diagnosis was proved by genetic methods.
Second case: diagnostic procedures of a 51-year-old female patient showed an ACTH producing mediastinal tumor; non radical surgical removal was performed due to tumorous infiltration of the blood vessels. Histology revealed well differentiated neuroendocrine carcinoma of thymus. The general condition of the patient became rapidly deteriorated and she died after the surgical intervetion soon at the intensive care unit.
In our presentation two cases of a very rare disease are to be demonstrated. The patient with MEN1 syndrome is still in a symptom and metastasis free period after 3 years of surgical removal of his two distinct neuroendocrine tumors and under a continuous SSA therapy. In the other case the rapid progression of the disease led to the death of the patient soon after the surgical intervention and before any further therapeutic procedure.

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P568

Expression of prolactin receptor in aldosterone-producing adrenal adenomas

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Scattered case reports have described patients who have been diagnosed with both primary hyperaldosteronism and prolactinoma. Prolactin receptor (*PRLR*) is known to be expressed in human adrenal cortex. Furthermore, *PRLR* mRNA and protein have both been detected in human adrenal tumors. It has also been shown that PRL treatment of adrenal cells is capable of stimulating aldosterone secretion. The contribution of PRL to the development of hyperaldosteronism is unkown. We hypothesize that a subset of adrenal adenomas may be stimulated to produce aldosterone due to elevated PRL sensitivity which occurs via increased *PRLR* expression. To begin to assess this, we identified a well-defined group of patients with aldosterone-producing adenomas. Tissue samples from adrenal adenomas as well as adjacent normal adrenal tissue were collected from 12 patients (six males and six females). A real-time RT qPCR assay was used to quantify the expression of *PRLR* mRNA in these samples. We found high *PRLR* mRNA expression in both tumors and normal adrenal tissue from APA patients. Strikingly, *PRLR* mRNA expression was higher than the reference gene, hypoxanthine–guanine phosphoribosyltransferase. There was no significant difference in *PRLR* mRNA expression between tumors and healthy adrenal tissue. In conclusion, we have no indication that expression of *PRLR* mRNA is upregulated in aldosterone-producing adrenal adenomas relative to non-tumoral adrenal tissue in APA patients. Further work is necessary to better understand the interplay between pituitary hormones and adrenal function and disease.

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P569

Patient with dissemination of neuroendocrine neoplasm of unknown origin and carcinoid syndrome: diagnostic and therapeutic difficulties

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Introduction
Serotonin producing neuroendocrine tumors are usually well differentiated, small lesions localised in the small intestine. Visualisation of the primary tumor might be difficult due to its small size.

Case report
A 52 years old man presented with diarrhoea and flushes. Ultrasound examination and computed tomography of the abdomen revealed numerous lesions in the liver. Gastroscopy, colonoscopy and magnetic resonance imaging did not reveal the primary tumor. On histopathological examination of the metastatic lesion poorly differentiated cancer of neuroendocrine origin was diagnosed. Patient was qualified to chemotherapy with cisplatin and etoposide, with no clinical response and no response on imaging examinations. Patient was referred to our center. Somatostatin receptor scintigraphy (SRS) revealed increased uptake of the tracer in liver metastases, in the lymph nodes of mesentery and in the single lymph node in the mediastinum. Owing to the symptoms of the carcinoid syndrome (diarrhoea, six to eight stoolsm per day and flushes three to four times per hour) treatment with long acting somatostatin analogue was started. Owing to still unknown primary ^{18}F-FDG/PET was performed. The examination revealed the primary tumor in the small intestine, which was excised. On histopathological examination neuroendocrine tumor of the small intestine with Ki67 $<2\%$ was confirmed. Owing to the advanced disease, ineffectiveness of chemotherapy and positive result of SRS patient was qualified to peptide receptor radionuclide therapy (PRRT). PRRT led to further improvement of clinical symptoms (diarrhoea, one to two stools per day and flushes, six to eight times a day). Imaging examinations are planned.
Conclusions
Above case report shows possible difficulties in searching for the primary lesion in case of patients with carcinoid syndrome with the use of different imaging modalities. Moreover it presents the known possibility of distinctions in grading between the primary tumor and metastases.

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P570

Uncertain clinical prognosis of pancreatic neuroendocrine tumour: case report

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Introduction
Despite development of diagnostic and therapeutic possibilities pancreatic neuroendocrine tumours remain still a clinical challenge.
Case report
A 31-year-old woman after cholecystectomy performed in 2007. MRI performed in November 2008 due to abdominal pain revealed tumour of the pancreas – $35\times 42\times 32$ mm. In May 2009 patient underwent partial excision of the pancreas. On histopathological examination neuroendocrine tumour NET G2 with Ki67 16% was found. Treatment with long acting somatostatin analogue was started. CT performed in October 2009 revealed lesion in the 7th hepatic segment – lesion was verified prior to the surgery as hemangioma. There was no pathological uptake visible in SRS performed in August and then in December 2009. The size of the lesion in the liver was stable on usg performed in February 2010. However USG examination in June 2010 showed additional three lesions in the liver. The progression of the liver changes was confirmed with CT. PET/CT with ^{68}Ga-DOTA-TATE revealed increased expression of the somatostatin receptors in the hepatic lesions. Patient did not accede for the surgery and was qualified to the radioisotope therapy. PET/CT performed two months after therapy revealed two additional hepatic changes. Patient was suggested again to undergo surgery. The right-sided hemihepatectomy was performed in October 2011. There was no recurrence nor metastases visible in further imaging examinations till November 2013, when the metastatic lesion in the 1st hepatic segment was revealed by ^{68}Ga-DOTA-NOC PET/CT and magnetic resonance imaging. Patient was referred to surgical department.
Conclusions
Above case report shows the necessity of rigorous follow-up of the patients with pancreatic neuroendocrine tumours of intermediate differentiation with uncertain clinical prognosis.

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P571

Androgens regulate gene expression of glucose transporters and glycolytic enzymes in prostate cancer cells

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Prostate cancer (PCa) is an endocrine tumor that presents distinct metabolic features associated with neoplastic development, namely in the transition from the androgen-dependent to the androgen-independent phenotype that characterizes advanced stages of prostate cancer. Recently, we have found that LNCaP (androgen-responsive) and PC3 (androgen-nonresponsive) PCa cells present distinct glycolytic metabolism profiles in consequence of altered gene expression and/or activity of glycolytic enzymes and transporters. Therefore, this study was designed aiming to examine the effect of androgens on gene expression of glucose transporters and glycolytic enzymes in androgen-responsive PCa cells. LNCaP cells were treated with 10 nM of 5α-dihydrotestosterone (DHT) for 12, 24, and 48 h. Glucose consumption and lactate production were determined spectrophotometrically using commercial kits. Expression of glucose transporters (GLUT1 and GLUT3), phosphofructokinase 1 (PFK1), lactate dehydrogenase (LDH) and monocarboxylate transporter (MCT4) mRNA and protein was analyzed by real-time PCR and Western Blot, respectively. LDH enzymatic activity also was determined. The obtained results demonstrated that androgens stimulation diminished the expression of both GLUT1 and GLUT3, and increased PFK levels. Also, the expression of LDH and MCT4 was diminished in LNCaP cells in the presence of DHT, which was concomitant with decreased enzymatic activity of LDH. In addition, we verified that androgenic regulation of genes associated with glycolytic metabolism underlies altered glucose consumption and lactate production in LNCaP cells. These findings demonstrated that androgens are modulators of glycolytic metabolism in PCa cells, which may represent a relevant aspect driven prostate tumor development.

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P572

Peptide receptor radionuclide therapy as neoadjuvant treatment

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Introduction
Peptide receptor radionuclide therapy is indicated in case of patients with disseminated neuroendocrine tumors and is usually considered as palliative treatment.
Case reports
55 years old man diagnosed with tumor of the pancreatic head. On laparotomy performed in June 2012 tumor was stated unresectable. Histopathological examination revealed the mixed adeno-neuroendocrine cancer (MANEC). Patient was qualified to chemotherapy with gemcitabine. However progression of the tumor size was visible after 4 months of therapy. Due to ineffectiveness of chemotherapy and positive result of somatostatin receptor scintigraphy, with increased uptake of the tracer in the solid part of the tumor, patient was qualified to peptide receptor radionuclide therapy. Imaging examinations (ultrasound examination, computed tomography, somatostatin receptor scintigraphy) performed after PRRT confirmed decrease of the tumor size (both solid and cystic part of the tumor) from 90 mm prior to the therapy to 43 mm after treatment. Patient was referred to surgical department.
61 years old woman with tumor of the pancreatic head. On laparotomy performed in February 2013 tumor was stated unresectable. Histopathological examination revealed neuroendocrine tumor of the pancreas with Ki67 5 – 10% (NETG2). Somatostatin receptor scintigraphy revealed increased uptake of the tracer in the tumor. Patient was qualified to peptide receptor radionuclide therapy. Treatment led to decrease of the tumor size from 80 mm prior to PRRT to 44 mm after the therapy. Patient was referred to surgical department.
Conclusions
Above case reports indicates that peptide receptor radionuclide therapy might be also considered as form of neoadjuvant treatment. Moreover the case of patient with mixed adeno-neuroendocrine cancer shows that peptide receptor radionuclide therapy might be also considered in case of ineffectiveness of chemotherapy.

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P573

CD56 immunohistochemical expression: a useful tool for the diagnosis of in thyroid carcinomas of follicular origin

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Introduction
CD56 (neural cell adhesion molecule/NKH1/LEU19 and LEU7/NHK-1) is an antigen related to follicular epithelium differentiation.
Materials and methods
We evaluated the expression of CD56 protein in normal follicular thyroid tissue, 15 non-neoplastic thyroid lesions (nodular hyperplasia–NH, Graves–Basedow disease (GB) and chronic lymphocytic/Hashimoto is thyroiditis (HT) and 38 thyroid neoplasias derived from follicular cells (25 PTC and 13 follicular neoplasias (five follicular adenomas (FA), two FA with Hurthle cells, two follicular carcinomas (FC), 1 Hurthle cell carcinoma (HCC) and three follicular tumors with uncertain malignant potential (FT-UMP), in our attempt to appreciate the value of this marker in differentiating PTC (including its follicular variant (FV)) from other follicular lesions/neoplasias. The IHC reactions were carried out on sections stained with the anti-CD56 antibody (clone 1B6), dilution 1:100, using the EnVision+Dual Link System-HRP (visualization with DAB). For the statistical analysis, the χ^2 test was used, values ≤ 0.05 being considered statistically significant.
Results
We noted CD56 expression in 28.95% of follicular tumors and 15.79% of PTC; CD56 immunoexpression differentiated PTC from non-neoplastic benign lesions (NH, GB and HT) ($P=0.017$; χ^2 test), as well as from follicular neoplasias (FC and HCC) ($P=0.0455$). The results were also significant when we compared CD56 expression in PTC with the one in FA, NH and HT ($P=0.0124$) and PTC–FV with non-malignant lesions (FA+NH+HT) ($P=0.0080$) or with non-tumor thyroid lesions (NH+HT+GB) ($P=9096655E-05$), respectively. We did not observe significant differences in the expression of CD56 when differentiating PTC–FV from classical PTC ($P=0.4362$). Solid cell nests were the only lesions in the thyroid gland with negative CD56 immunophenotype, similar to PTC.
Conclusions
CD56 proves to be a useful marker in the diagnosis of PTC, including PTC–FV and microcarcinoma; the absence of CD56 expression in PTC–FV can be a useful biomarker in differentiating PTC–FV from other thyroid nodules with follicular pattern.

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P574

A clinical case of effective treatment of giant prolactinoma in patient with morbid obesity

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Introduction
Numerous literature sources indicate the potential role of hyperprolactinemia in the development of obesity. Prolactin modulates the functional activity of several enzymes and transporters in adipose tissue and islets of Langerhans, potentially influencing fat and glucose metabolism. On the other hand, elevated prolactin level may induce eating disorders due to dysfunction of dopaminergic regulation of the CNS. We present a clinical case of a man with morbid obesity and giant prolactinoma which was successfully treated by high-dose cabergoline.
Clinical case presentation
A 30-year-old man presented with severe cephalgia, visual disturbances, hyperprolactinemia (PRL 12000 IU/l, no macroprolactinemia), endo-supra-laterosellar macroprolactinoma (31.3×25.5×25 mm). The patient was consulted by a neurosurgeon; the question about operation was resolved negatively due to high risk of surgical intervention and almost full loss of vision (OD=0 and OS=0.1). Administration of bromocriptine with maximum dose 12.5 mg/day for 3 years did not result in significant clinical or laboratory improvement. After that cabergoline therapy was started with gradually increasing doses up to 4.5 mg/week. Control MRI tomograms showed a good positive dynamics of adenoma size and prolactin level without complete normalization. After 5 years of cabergoline treatment MRI revealed 'empty sella'. Unfortunately, visual function didn't recover because of long period of optic nerves compression. Increase in body weight was noted before the diagnosis of prolactinoma presumably coinciding with the onset of hyperprolactinemia with no significant elevation during the further period of active treatment with dopamine agonists. At present, patient's BMI is 50.8 kg/m^2, without impairment of glucose metabolism. The patient got diet instructions and initiated treatment with testosterone ethers.
Conclusion
This clinical observation illustrates potential relationships between prolactin and obesity and positive influence of dopamine agonists on fat metabolism among patients with hyperprolactinemia.

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P575

Chemoembolization as a locoregional treatment for metastatic disease on a liver transplant from a bronchial carcinoid neuroendocrine tumor

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Introduction
We present the results of chemoembolization used as a locoregional treatment for liver metastases (on a transplanted liver) from a bronchial carcinoid neuroendocrine tumor with stage IV disease progression.
Case report
A 60-year-old man diagnosed of bronchial carcinoid NET in 2002, underwent surgery by lung lobectomy and excision of lymph node metastases. Treated also with somatostatin analogues (SA) after subsequent discovery of liver metastases with initial stabilization. 2005, due to the finding of elevated biomarkers and liver uptake on the Octreoscan/PET, he received a liver transplant with subsequent disease stabilization without SA. In 2008 he was still free from liver affection, but he had bone metastases, so he was treated with radiopharmaceutical 177 Lutetium–Octreotate. In 2011 he showed mediastinum uptake on the Octreoscan/PET–CT, so he underwent an exploratory thoracotomy and subtotal mediastinal lymphadenectomy, finding NET on the pathology. In 2012 he relapsed with metastases on the transplanted liver, and was treated with mTOR inhibitors. Despite this treatment, he continued with disease progression (5–10% Ki-67 index, indicative of well differentiated NET), so he was considered a candidate for debulking chemoembolization therapy, alongside palliative radio-therapy for bone metastases. In June 2013, the first chemoembolization was performed: segmental branches of the right hepatic lobe (RHL) were accessed by selective arteriography, with embolization of RHL nodules with microspheres loaded with adriamycin. The final angiographic control showed a significant decrease in the number of hypervascular nodules. A second chemoembolization was performed on the left hepatic lobe nodular lesions in October 2013. Overall, there was a good clinical, radiological and analytical response.
Conclusion
Chemoembolization is a valid treatment option for locoregional metastatic liver disease of well differentiated NETs when systemic treatment has failed to stabilize the disease. Although it is not curative, it does seem to improve both survival and qualitiy of life of these patients, as described in previous studies.

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P576

Correlation between atypical pituitary adenomas and Ki-67 Li: clinical and prognostic aspects

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Introduction
In 2004, the WHO defined atypical pituitary adenomas (APAs) those with Ki-67 >3%, excessive p53 expression and increased mitotic activity. The usefulness of this classification is still controversial.
Aim
To compare the clinical and prognostic features in a series of typical and atypical pituitary adenomas.

Materials and methods
We retrospectively reviewed 343 consecutive PAs. APAs represented 18.7% of the cases. TPAs represented 81.3% of the cases. All patients were operated on in the Department on Neurosurgery at our institution and followed up in the last 9 years at the Hypothalamic-Pituitary Disease Unit of the same institution. APAs and TPAs did not differ for age at diagnosis, gender, tumor size and extension. ACTH-secreting PAs were more frequent in APAs than TPAS (15.6 vs 6.8%, $P=0.02$). Radical surgery occurred in 51.5% of APAs and in 71.2% in TPAs ($P=0.003$). Partial surgery was more likely in APAs than TPAs (OR: 0.43; 95% CI: 0.247–0.749). From the 231 patients that underwent radical surgery, recurrence occurred in 42 cases: 7/33 APAs (21.2%) and 35/198 TPAs (17.7%), $P>0.05$. Disease-free survival time (DFST) did not differ between APAs and TPAs (HR: 1.508; 95% CI: 0.65–3.497). According to our experience, a Ki-67 value above 1.5% correlated better with partial reception and with a worse DFST. For this reason, we compared recurrence risk and DFST in PAs with KI-67 $\geq 1.5\%$ and PAs with Ki-67 $<1.5\%$. Among the 232 patients that underwent radical surgery, recurrence occurred in 25% (19/75 cases) of PAs with Ki-67 $\geq 1.5\%$ and in 14.7% (23/156 cases) of PAs with Ki-67 $<1.5\%$ (HR: 2.166; 95% CI: 1.154–4.064). PAs with Ki-67 $\geq 1.5\%$ showed a worse DFST as compared to PAs with Ki-67 $<1.5\%$ (HR: 2.166; 95% CI: 1.154–4.064).
Conclusion
In our experience, APAs and TPAs did not differ for recurrence and DFST, while PAs with Ki-67 $\geq 1.5\%$ showed an higher recurrence risk and a worse DFST. We propose that a Ki-67 $\geq 1.5\%$ may be useful as prognostic marker.

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P577

Patient-reported outcomes associated with lanreotide Autogel (LAN-ATG) for symptom control of carcinoid syndrome in gastroenteropancreatic neuroendocrine tumour patients: results of SYMNET, a large International Multicentre Observational Study

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Introduction
Somatostatin analogues are widely used to reduce the incidence and severity of carcinoid syndrome symptoms. However, their impact on patients' satisfaction with symptom control needs further investigation. SYMNET was a large international multicentre observation study that assessed PROs during LAN-ATG treatment of carcinoid syndrome in gastroenteropancreatic neuroendocrine tumour (GEP–NET) patients.
Methods
At routine clinic visit, patients with diarrhoea related to carcinoid syndrome and receiving LAN-ATG for >3 months were asked to complete PRO questionnaires on satisfaction and symptoms associated with their treatment. Investigators also assessed patients' medical records to identify patient characteristics that were potential predictors of treatment satisfaction.
Results
Of 273 patients enrolled, 56% were males, 57% were aged >60 years, 66% had small bowel primary tumours, and 80% had liver metastases. Prior to the study, 66% had surgery and 23% other anti-tumour therapy within last 3 months. Mean time since diagnosis was 4.4 years. Mean LAN-ATG treatment duration was 21.7 months and median dose 120 mg/month on study day. Most patients (76%) were satisfied with diarrhoea control, and flushing control (73%). More patients indicated no, minimal, or mild diarrhoea at study visit (75%) than did before treatment (33%). Most (79%) patients reported diarrhoea was improved overall with LAN-ATG. Investigators identified a clinically relevant decrease in stool frequency since treatment initiation (median: 4–2 episodes/day). Statistically significant decreases (McNemar paired tests, $P<0.001$) were seen in the proportion of patients with urgency (73–41%), leakage (21–9%), and associated pain (37–4%). Predictors of satisfaction with diarrhoea control were initial stool leakage and non-small bowel primary localization.
Conclusions
GEP–NET patients reported favourable symptom control with LAN-ATG treatment. Improvements in PROs were consistent with those on investigators' medical assessments. Patients' satisfaction with symptom control on LAN-ATG may be supported by associated factors.

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P578

Antiproliferative effects of lanreotide Autogel in patients with enteropancreatic neuroendocrine tumours: results of CLARINET, a large international phase 3 study

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Introduction
Data demonstrating antiproliferative effects of somatostatin analogs (SSAs) in enteropancreatic NETs are limited; only one prospective trial so far has shown this for patients with midgut tumors and low hepatic tumor load (HTL). CLARINET is the first large phase 3, randomized, placebo-controlled trial evaluating such effects for the SSA lanreotide in patients with non-functioning enteropancreatic NETs.
Methods
Patients who had well/moderately differentiated, with Ki67 $<10\%$, non-functioning enteropancreatic NETs, and no SSA or other medical therapy within the last 6 months, received lanreotide Autogel 120 mg ($n=101$) or placebo ($n=103$) every 4 weeks for 96 weeks or until progression/death. The primary endpoint was progression-free survival (i.e., time to progression using RECIST, or death) based on centrally assessed CT scans.
EudraCT: 2005-004904-35; ClinicalTrials.gov: NCT00353496.
Results
At enrolment, primary tumor locations included pancreas (44%) and midgut (36%); 96% had stable disease and 84% were treatment-naïve; 30% had Ki67 3–10% (WHO grade 2); and 33% had HTL $>25\%$. Lanreotide treatment significantly prolonged PFS vs placebo (stratified logrank $P=0.0002$): median PFS was not reached with lanreotide vs 18 months with placebo (HR 0.47; 95% CI 0.30–0.73). At 2 years, 62% on lanreotide vs 22% on placebo had not progressed or died. Similar results for lanreotide vs placebo were seen in patients with HTL $>25\%$ (logrank $P=0.017$; median PFS 24.1 vs 9.4 months; HR 0.45; 95% CI 0.23–0.88) and in those with grade 2 tumors (logrank $P=0.024$; median PFS not reached vs 12.1 months; HR 0.45; 95% CI 0.22–0.91). Lanreotide showed favorable safety/tolerability consistent with its known safety profile: treatment-related AEs occurred in 50% on lanreotide vs 28% on placebo (most frequent event was diarrhea, 26 vs 9%).
Conclusions
This new evidence demonstrates the antiproliferative effects of lanreotide Autogel as shown by a clinically significant increase in PFS in enteropancreatic NET patients.

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P579

Efficacy and safety of lanreotide Autogel treatment for carcinoid syndrome in patients with gastroenteropancreatic neuroendocrine tumors: results of ELECT, a large multinational phase 3 study

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Introduction
Somatostatin analogues (SSAs) are the mainstay treatment for carcinoid syndrome. ELECT is a large multinational phase 3 study evaluating rescue therapy use as a measure for control of carcinoid syndrome symptoms with LAN-ATG.

Methods
Eligible patients had histologically-confirmed GEP-NETs and history of carcinoid syndrome, and were SSA-naïve or responsive to conventional doses of octreotide LAR ($\leq$30 mg/4 weeks) or short-acting ($\leq$600 µg/day s.c.). The study comprised a 16-week randomized double-blind phase (LAN-ATG 120 mg ($n=59$) vs placebo ($n=56$) every 4 weeks), followed by a 32-week long-term open-label phase on LAN-ATG. Short-acting octreotide was available as rescue for breakthrough symptoms throughout the study. Primary endpoint was % of days of rescue octreotide use during the double-blind phase. The study was designed to have 90% power to detect a treatment difference of 30%. Results of the double-blind phase only are presented (open-label phase still ongoing).
Results
Of the study population, 83 (72%) had symptoms for $\geq$1 year, and 51 (44%) had no prior SSA use. Mean (95% CI) % of days with rescue medication use was significantly lower with LAN-ATG (34% (25, 42%)) vs placebo (49% (40, 57%)), absolute difference −15% (−27, −3%), $P=0.02$; however, the pre-defined difference was not met. Complete/partial success ($\leq$3 days use) rather than failure (>3 days use) was more likely with LAN-ATG than placebo (OR 2.4; 95% CI 1.1–5.3; $P=0.04$). Treatment related AEs occurred in 15 (26%) LAN-ATG patients vs 11 (19%) placebo patients; Few of these were serious (2 (3%) vs 5 (9%)) or led to study withdrawal (1 (2%) vs 1 (2%)); and were most commonly GI disorders (9 (16%) vs 5 (9%)).
Conclusions
LAN-ATG significantly reduced need for short-acting SSA use and had a favourable safety/tolerability profile confirming its positive benefit-risk profile.

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P580

Plasma free metanephrine, normetanephrine and 3-methoxytyramine for the differential diagnosis of pheochromocytoma and paraganglioma

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Background
Pheochromocytoma (PHEO) and paraganglioma (PGL) of abdominal origin secrete catecholamines which are metabolized to metanephrines. Head-and-neck paraganglioma (HNPGL) are considered as non secretary tumors.
Objectives
To find the utility of plasma free metanephrine (MN), normetanephrine (NMN) and 3-methxytyramine (3-MT) for the differential diagnosis PHEO/PGL after excluding MEN2 and VHL patients.
Methods
A total of 79 consecutive patients attending the AIIMS clinics based on clinical symptoms, histological findings and MRI reports were diagnosed with PHEO/PGL (benign ($n=59$), metastatic ($n=9$), MEN2 ($n=7$) and VHL ($n=4$)). 65 healthy age matched subjects were taken as controls. The subjects with MEN2 and VHL were excluded from the study. Plasma free metanephrines (MN, NMN and 3-MT) were estimated in 64 patients with PHEO/PGL by HPLC technique using ECD after solid phase extraction.
Results
The results of this study showed that plasma MN and NMN levels were high in 10 and 33% of patients with HNPGL where as in controls plasma MN and NMN were high in 3.9 and 1.5% respectively. The 3-MT was high in 53.3% of the patients as compare to controls (6.2%). In patients with PHEO/abdominal PGL, MN, NMN and 3-MT were high in 48, 96 and 53% respectively. The mean levels of MN, NMN and 3-MT were 167 ± 260, 659 ± 543 and 2.732 ± 4.325 pg/ml respectively in HNPGL and 1.917 ± 3.447, 7.150 ± 11.454 and 4.752 ± 7.329 pg/ml respectively in the patients with PHEO /abdominal PGL as compare to controls (110 ± 195, 255 ± 224 and 590 ± 690) pg/ml respectively.
Conclusions
This study concludes that plasma NMN is useful biochemical marker for diagnosis of PHEO/ abdominal PGL after exclusion of patients with MEN2 and VHL, as compared to MN and 3-MT, with high sensitivity (96%) and specificity (98%). Plasma 3-MT can be useful in the identification of patients with HNPGL.

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P581

Is early repeat surgery a feasible concept for potential incomplete resection in acromegaly?

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Transsphenoidal surgery is the treatment of choice for acromegaly. Cure is defined by normalization of age-related IGF1 and sufficient suppression of GH in the oral glucose tolerance test (OGTT). We investigated, if early postoperative hormone testing gives reliable information whether complete resection of a tumor was achieved and compared these findings with further follow-up data.
So far, 22 patients underwent OGTT within a week after surgery, starting April 2013. Sixteen patients were surgically classified as complete resection, in five patients the intraoperative finding remained unclear regarding completeness, one patient underwent partial resection.
Eleven of 16 patients with 'complete resection' showed adequate GH suppression below 1 µg/l in the early postoperative phase (69%). Follow-up by IGF1 and OGTT is available in seven patients so far, which confirms the initial findings. In three patients, the GH suppression was formally inadequate within a week, however, became physiological during further follow-up (19%). In the five patients with unclear resection grade due to invasive growth, two showed adequate suppression of GH during early OGTT and during follow-up (40%). In the remaining 3 patients, follow-up is pending.
The patient with incomplete resection showed no suppression of GH post-operatively as well as during follow-up, IGF1 remained pathological.
These preliminary results show, that OGTT in the early postoperative stage is not sufficient to identify residual disease, as previously shown by Kristof *et al.*, 2002. However, OGTT seems efficient to predict cure in 'positive' findings. So far, we lack a method to justify early repeat surgery in acromegaly in unclear cases. Moreover, these results have to be taken into account prior to initiation a medical therapy after surgery.

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P582

Eleven base pair (AACACTCTAGC) deletion of SDHB Ex-4 from c.325 to c.335 in the patient with malignant Vaginal Paraganglioma – A case report

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Background
Pheochromocytoma (PHEO) and paraganglioma (PGL) are the tumors of adrenal medulla and extra adrenal ganglia respectively. Most of these PHEO/PGL are benign and may become malignant, if remain undiagnosed/untreated for a longer time. Vaginal PGL are extremely rare. There is not much published literature on vaginal PGL.
Objective
To carry out biochemical and genetic analysis of the patient with MIBG negative malignant vaginal PGL.
Methods
Blood sample was collected from the patient lying supine for at least 30 min. Plasma free metanephrines (MN, NMN and 3-MT) were estimated using HPLC. SDHB, C and D genes were sequenced after amplification from the DNA extracted from peripheral blood.
Results
22 years female attending endocrine clinic complained of headache, palpitation for 6 years. She had visual disturbance for 1 month. She had tender firm mass involving anterior vaginal wall, hard non tender mass along right lateral pelvic wall. Her MIBG scan was done and it was found negative. Her NMN was 6.800 pg/ml (reference range <800 pg/ml). Owing to high NMN levels MIBG and DOTANOC scan was done. MIBG scan was negative and DOTANOC scan showed increased uptake in pelvic mass, along bilateral sympathetic chain and in left femur. MRI showed solid mass arising from proximal vagina extending along right internal iliac vessels.USG abdomen showed B/l polycystic ovaries, vaginal mass 4.5×4.5 cm and Rt. parametrical mass 2.8×2.9. Her genetic analysis showed 11 bp (AACACTCTAGC) deletion of SDHB Ex-4 from c.325 to c.335. Her family history was negative for the disease from maternal and paternal side. Genetic analysis of her family members was also done. Her father was found positive for the same deletion.

Conclusion
The biochemical and genetic analysis should be carried out in the patients with MIBG negative imaging. In this case the mutation showed variable expression.

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P583

^{99m}Tc-GLP-1 scintigraphy, an efficient method for the detection of insulinoma: results of 3 years' experience

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Introduction
The aim of this study was to assess the diagnostic efficiency of [Lys^{40}(Ahx-HYNIC-^{99m}Tc/EDDA)NH_2]-exendin-4 scintigraphy in the detection of hardly detectable or not diagnosed by other available method insulinomas.
Materials and methods
37 patients (24 women and 13 men, mean age 46.5 ± 17.8 years, min. 16.0 years, max. 77.0 years) were enrolled in this study. There were 32 patients with clinical and biochemical symptoms and signs of insulinoma, one patient with malignant insulinoma, one patient with suspected local recurrence of malignant insulinoma (MEN1) and three with nesidioblastosis. In all patients prior examinations (CT/MRI/SRS) were negative or equivocal. The lyophilized kit provided by Radioisotope Center POLATOM was used for preparing the tracer. Whole-body and SPECT/CT scans at two points time points were performed.
Results
In 27 cases with suspicion of insulinoma a focal uptake in the pancreas was found – classified as insulinoma. In four negative cases reactive hypoglycaemia was diagnosed. In one case exogenous stimulation of insulin level by patient was revealed. In one case with malignant insulinoma pathological accumulation of the tracer was found only in the region of local recurrence. The GLP-1 study was negative in the other malignant insulinoma patient. In two patients with suspected nesidioblastosis diffuse accumulation of tracer was observed. In one case with suspicion of nesidioblastosis, a focal accumulation of the tracer was observed – histopathology revealed coexistence of insulinoma and nesidioblastosis.
Conclusion
^{99m}Tc-GLP-1 receptor scintigraphy is a promising diagnostic tool for patients with clinical symptoms of insulinoma. It enables the localization of even very small tumours with excellent sensitivity and proper imaging is the most important step for successful surgery and complete patient recovery.

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P584

The first experience of video-assisted resection of the thyroid gland in the Republic of Kazakhstan

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Background
Videoassisted resection of the thyroid gland with unilateral nodular lesions of the thyroid gland, as compared to the conventional method is a safe and effective method.
Materials and methods
Patient M, a woman 30 years old, BMI 30.37. Admitted with complaints of discomfort and a feeling of constriction in the neck, mild shortness of breath on exertion. The cervical lymph nodes were not enlarged. According to the USI are found nodes in the right lobe of the thyroid gland sizes up to 2.5×2.5 cm. According to the needle biopsy, the conclusion: cancer cells are not found. Thyroid hormones are normal.
Performed videoassisted right gemithyroidectomy sided with the removal of the isthmus. Intraoperative: under endotracheal anesthesia, skin incision is made 3.0 cm parallel to the right clavicle, which is set wound protector, on the left side below the clavicle has two 5 mm ports.
Then 'Lifting system' is installed for skin traction. Has been accessed and the mobilization of the right lobe of the thyroid gland with the isthmus. Histological conclusion: cystic nodular colloid goiter.
Results
The operative time was 150 min. Blood loss was <10 ml. In the postoperative period we observed no palsy of the recurrent laryngeal nerve, hematoma as well as no pain. The patient's condition on the second day after the operation is satisfactory.
Conclusion
Videoassist minimal-invasive thyroidectomy has distinct advantages over traditional open resection, as a small trauma, better visualization of the thyroid gland and its surrounding structures, reducing the volume of intraoperative blood loss. As well as the lack of the need for a large number of ligatures which are alien and impair healing of tissue. Reduces length of hospital stay, significantly reduced pain in the postoperative period and good cosmetic effect.

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P585

Combined therapy PRRT with long acting somatostatin analogue: results of 7 years' experience

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Introduction
The aim of this study was to assess the survival rate of patients with disseminated or inoperable neuroendocrine tumors (NETs) after PRRT with the use of ^{90}Y-DOTATATE combined with long acting somatostatin analogue.
Materials and methods
72 patients were treated with PRRT in our Department. The ^{90}Y-DOTATATE therapeutic activity was calculated per total body surface area up to a total of 7.4 GBq/m^2 administrated in three to five cycles, repeated every 1–9 weeks. After PRRT, patients have been further treated with cold long acting somatostatin analogues to the progression of the disease.
Results
Out of 72 ^{90}Y-DOTATATE treated patients, 22 died after completing the therapy, among them two due to myocardial infarction. After 12 month follow-up, stabilization of disease was observed in 63%, partial remission in 25%, and progression in 12% in this group of patients. The progression free survival (PFS) was found to be 41.27 months and the event-free survival (EFS) – 37.73 months. The median overall survival (OS) was not reached. According to the literature (Ćwikła *et al.* 2010) in group of 57 patients treated by ^{90}Y-DOTATATE up to a cumulative activity of 15.2 GBq PFS and OS was about 17 and 22 months respectively. During follow-up, transient decrease of PLT, WBC and haemoglobin values was observed. An increase of creatinine level and decrease of GFR values in the observation period were found, but these were clinically insignificant symptoms of transient nephrotoxicity.
Conclusion
PRRT and further treatment with long acting somatostatin analogues may extended the survival of disseminated patients with NETs. Long-term patients benefit in the form of symptomatic relief and tumour mass reduction after ^{90}Y-DOTATATE therapy was also observed.

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P586

The anti-proliferative effect of anti-EGFR tyrosine kinase inhibitor in combination with mitotane on H295R adrenocortical cancer cells

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Introduction
Adrenocortical carcinoma (ACC) is a rare disease with a poor prognosis and limited therapeutic options. Mitotane is considered as a first-line therapy but only 30% of the patients showing an objective tumour response.
Erlotinib and gefitinib (tyrosine kinase inhibitors – TKI) inhibit the epidermal growth factor receptor (EGFR), which is highly expressed and occasionally mutated in various cancers. EGFR expression was found to be a good discriminator between malignant and benign adrenal tumours. EGFR mutations in exons 18–21 have been found in 3–10% of ACC cases (but not in the H295R ACC cell line) although their functional significance remains unknown.
Aim
The aim of this study was to assess whether erlotinib or gefitinib (used alone or in combination with mitotane) inhibit ACC cell proliferation in a pre-clinical setting.
Materials and methods
The proliferation rate of the H295R ACC cell line was assessed by Alamar blue assay: optimal time points for determination of cytotoxic effect of the inhibitors were 72 and 96 h of incubation.
Results
Mitotane at a concentration of 10 μM decreased the proliferation rate by 23%.
Erlotinib inhibited cell proliferation more effectively than gefitinib, causing a cytotoxic effect of 32 and 43%, vs 6 and 12% for gefitinib, after 72 and 96 h of incubation respectively ($P<0.001$). The combination of mitotane with the EGFR inhibitors showed an additive effect on cell proliferation (41 and 45% for mitotane + erlotinib, and 29 and 32% for mitotane + gefitinib, at 72 and 96 h, respectively).
Conclusions
Erlotinib inhibits cell proliferation more potently than gefitinib, and causes higher H295R cells cytotoxicity in combination with mitotane. Combined therapy with agents targeting the EGFR and standard treatments may have the potential to improve the treatment of ACC patients. Given the lack of somatic mutations in this cell line, the potential mechanism(s) of sensitivity to anti-EGFR TKI is currently being investigated.

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P587

Gonadal tumor incidence in 45,X/46,XY and 46,XY female patients: experience from one clinical center

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Type II germ cell tumors are predictable complications in patients with disorder of sex development (DSD) and with Y chromosome present. The risk of tumor development varies significantly between subsets of DSD and in some cases early gonadectomy is perceived as overtreatment.
The aim of the study was to analyze the gonadal tumor incidence in 45,X/46,XY and 46,XY patients who were reared as female and managed at single institution between 1997 and 2013.
Patients and methods/results
15 patients, 7 with 45,X/46XY diagnosed as Turner syndrome (TS), eight with 45,XY DSD caused by androgen insensitivity syndrome (AIS) or gonadal dysgenesis (GD). The mean age of diagnosis in 45,X/46,XY TS and for the patients with 46,XY DSD were 6.63 ± 6.0 and 13.56 ± 5.73 years respectively ($P<0.05$). Gonadectomy were performed in 14 of 15 patients: in 7/7 TS patients (mean age 7.65 years, required before GH treatment), in 3/4 with AIS and in 4/4 with GD (in 6/7 within 1 year after diagnosis). 27 gonads were evaluated by histopatology. Gonadoblastoma was found in 2/13 gonads of TS patients. Gonadoblastoma with dysgerminoma was detected in 2/8 gonads of GD patients. Leydig-Sertoli cell tumor was described in 2/6 AIS gonads (in one patient). There were no evident clinical indicators of gonadal tumor risk in 45,X/46,XY and 46,XY female patients.
Conclusion
The risk of gonadal tumor was estimated at 14.8%. Further search for useful clinical/lab markers of individual tumor risk are urgently needed.

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P588

Ovarian tumors in endocrinology: about a series of 17 cases

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Introduction
The ovarian tumors are benign or malignant, primary or secondary proliferative processes, cystic aspect, solid or vegetating, whose growth is not directly related to a Hormonal dysfunction. They can grow at the coating tissue, be embryonic or endocrine origin.
Aim
Assess the frequency of ovarian tumors and clarify their phenotypic and evolutionary characteristics.
Population and methodology
This is a retrospective study about patients with ovarian tumors and hospitalized between 1982 and 2013
Results
17 cases were identified. Mean age was 28 years ± 1.2. Three patients had an age <10 years and three between 13 and 15 years reasons for consultation were hyperandrogenism (60%), tumor syndrome (30%) precocious puberty (10% cases). Ovarian tumors of children and adolescents are secreting in three cases. They are revealed by pelvic pain in 80% of cases. The average tumor size was 6.4 ± 1.2 cm with suspicious aspect of radiology in 33% of cases. The histological types found are teratoma (40%), arrhénoblastome (20%) tumor granulosa (10%), mucinous cystadenocarcinoma and dermoid cyst (20%) we found one ectopic corticossurénalome and one goiter in ovarian. tumors were germline. In all children 83% of tumors were treated surgically. Monitoring were decided in other cases (teratomas) 33% of cases were neoplastic requiring additional chemotherapy. The outcome was variable. Bilateralization (one granulosa tumor and two deaths (adrenocortical, arrhénoblastome) A cure was observed in other cases.
Discussion and conclusion
Ovarian tumor is difficult disease clinically, histologically and prognostically. Cancer accounts for 25–35% of etiologies. Surgical exploration affirm the cancerous nature and specify the stage of evolution. The ovarian tumors can occur at any age over puberty and before menopause. They are often discovered during a pelvic ultrasound, or pain, rarely menstrual disorders. Ovarian tumors are rare in children, 2/3 are benign in nature and germline.

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P589

Asymptomatic advanced neuroendocrine ovarian tumor: case report

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Introduction
Incidence of neuroendocrine neoplasms is still growing very rapidly. Many of these tumours are long term asymptomatic, definitive diagnose is confirmed in very advanced stage and make treatment difficult. Our case report illustrates diagnostic contribution of endoscopic adrenal biopsy.

Our patient was a woman, 68 years old in time of diagnosis, with good quality of life. One year before she was undergone hysterectomy with bilateral adnexectomy for postmenopausal bleeding. Small ovarian neuroendocrine tumour (G1, MiB1 $<5\%$) with small parts off benign Brenner's tumor was found in right ovary. Postoperative octreotide scan was found adrenal gland tumours on both sides (size 2 and 3 cm), not accumulating somatostatine analogue, suspected from feochromocytoma.
Patient was completely asymptomatic, with mild hypertension treated with monotherapy, mild and stable hypothyroidism and chronic asthmatic bronchitis, treated with inhalation corticosteroid.
Hormonal screening of adrenal function did not reveal any abnormality, feochromocytoma was excluded by low levels of plasmatic metanephrines and only pathologic finding was slightly elevated chromogranine A (203 ng/ml). Therefore, we performed adrenal biopsy (by uncomplicated esophagogastroduodenoscopy with transduodenal biopsy), from left adrenal gland (anatomically more accessible) was gained successful sample for cytological and histologic assessment – microscopically were found cell clusters with hyperchrome nuclei with anisonucleosis und small amount of cytoplasm, made diagnosis of neuroendocrine tumour metastasis almost certain.
According to this result, palliative chemotherapy (etoposide + carboplatine) was started and patient is still without symptoms and disease is stabilised.
Conclusion
Endosonography-guided biopsy could be useful tool in examining patients with adrenal tumours of unknown origin and could help to earlier diagnostics.

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P590

Analysis of factors affecting the repeatability and reproducibility of elastographic measurements of thyroid nodules

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Background
Elastography is an ultrasound technique that allows to predict risk of malignancy of examined lesion by assessing their stiffness. Its effectiveness in thyroid nodules is equivocal which may result from insufficient standardization.
Aim
Analysis of factors affecting the repeatability and reproducibility of elastographic measurements of thyroid nodules.
Methods
124 nodules in 118 patients were analyzed. Elastographic measurements were made qualitatively by using the 4-grade elastic score (ES) and quantitatively by evaluating the strain ratio (SR) between the nodule and the surrounding tissue. Reproducibility was tested by three investigators. Influence of the following factors on SR and ES was examined: imaging section (transversal/longitudinal), location of the nodule (isthmus/other), presence of other lesions superficially to the examined nodule, thickness of the fatty tissue ($\leq$5 mm/$>$5 mm), size of the nodule, its distance from the skin surface ($\leq$10 mm/$>$10 mm), percent of the cystic part in nodule ($\leq$25%/25–50%). Furthermore, influence of ultrasonographic malignancy risk factors (MRF) was analyzed. Intraclass correlation coefficient (ICC) was used as a measure of consistency for SR and coefficient κ Cohen's – for ES.
Results
Good mean repeatability and moderate mean reproducibility of ES assessment ($\kappa=0.47$ and 0.38, respectively; $P<0.0001$ both) as well as very good mean repeatability and good mean reproducibility SR assessment (ICC = 0.73, $P<0.0001$ and ICC = 0.53, $P<0.0005$) were observed. Blurred nodule's margins decreased reproducibility of SR (ICC = 0.510 vs 0.478, $P<0.0001$) and ES ($\kappa=0.39$ vs 0.35, $P<0.0005$). Other factors, especially other MRFs did not affect reproducibility and repeatability of elastography in the examined model (nodules $<$25 ml, located not deeper than 25 mm, the fat tissue thickness $<$15 mm, percentage of cystic part $<$50%).
Conclusion
Elastography in relation to the thyroid nodules has satisfactory repeatability and reproducibility of measurements. The presence of MRF, apart from blurred margin of the nodule, does not significantly affect elasticity measurements.

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P591

Should unifocal papillary thyroid microcarcinoma be treated as much radically as multifocal one?

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Introduction
Multifocal papillary thyroid microcarcinama (PTmC) has been considered as more aggressive than the unifocal one.
Aim of the study
This paper aims to compare this two groups considering histopatological sign of aggressivity, presence of inflammation and radioiodine uptake.
Materials and methods
The analysis concerned 81 patient with microcarcinoma (PTmC) selected from group of 961 (8%) diagnosed and treated in conventional way because of thyroid carcinoma. Patients were divided into three groups: S – one focus, diameter $\leq$10 mm ($n=45$); MS – multifocality, total diameter $\leq$10 mm ($n=22$); MB – multifocality, total diameter $>$10 mm ($n=14$). Histopatology, level of anti-thyroglobulin antibody (a-TG) and radioiodine uptake were analized.
Results
Sensivity of FNAB was significantly lower in MS as compared to S or MB. Percentage of cases with capsule's infiltration, angioinvasion and neck nodular metastases was the most highest in S respectively (62, 36, 11), MS (27, 18, 5) and MB (36, 7, 7). In multifocal cases capsule's infiltration occurred more often in MB while angioinvasion was more frequent in MS. Both groups were similar in respect of neck nodular metastases' presence. Presence of increased a-TG level was similar in S and MB but less frequent in MS while mean a-TG level was the highest in MS and lower but comparable in S and MB. Radioiodine uptake was comparable in all groups.
Conclusions
i) Inspite of the fact, that multifocality is believed to be associated with increased malignancy in analized group the signs of invasiveness were significantly more frequently observed in unifocal PTmC.
ii) Multifocality alone rather than total focuses' diameter should be considered as a potential indicator of increased risk of invasiveness of PTmC.
iii) Relatively high incidence of multifocality may justify total thyroidectomy as a treatment of PTmC.

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P592

Pancreatic neuroendocrine tumour with a silent long evolution: case report

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Pancreatic neuroendocrine tumors (pNET) represent 1.3% of pancreatic tumours, $\sim$65% patients presenting with metastatic/unresectable disease. Clinically, pNET may be asymptomatic, accompanied by carcinoid syndrome or abdominal pain. Patient N.A. aged 73, with a history of hemorrhagic pancreatitis, was diagnosed in 2003 with a hyperechoic heterogeneous solid pancreatic tumour of 28/28 mm. No therapy/monitoring were proposed. After 7 years of asymptomatic evolution, the patient was hospitalized for diffuse abdominal pain; abdominal CT described a solid tumour in the pancreatic corpus and isthmus and lymphadenopathic block. The tumor size, the adherences and the risk for vital vessels and nerves made the surgical intervention impracticable. Pathological exam (laparoscopic biposy) described a carcinoma metastasis, diffuse positive for cytokeratin AE1/AE3, chromogranin A, synaptophysin and Ki67 positive in 5–6% cells, markers which advocated for a well differentiated neuroendocrine carcinoma. Blood markers confirmed a secretory pNET. Treatment with somatostatin (Sandostatin LAR) was started. For 2 years he had a good evolution without clinical symptoms, with diminution of plasmatic markers (chromogranin A = 33.3 ng/ml) and a moderate reduction of tumour size. Sugical intervention was proposed but the patient refused it. Since then (in 12.2011 and 03.2013), he presented two acute episodes, with severe anemia, hypoglicaemia and alteration of general status, with good response to symptomatic treatment.

Conclusions
Incidental discovery of pancreatic tumour, asymptomatic for a long period of time (7 years) resulted in missing best time for surgery, usually the asymptomathic phase for pNET being of 1–2 years. Most pNET present, as our patient, at an advanced stage, the median survival time being 24 months. In spite this, our patient had a longer good evolution. Thus, we may suppose that, treated on time, he might have a better longer disease free period. This case emphasizes the importance early investigations of silent incidentalomas.

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P593

IGF1 gene polymorphism and thyroid cancer

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Aim
Several studies suggested that there is a relationship between serum levels of IGF1 or their polymorhisms and some cancer types. The genetic polymorphism in the region of IGF promoter region which is composed of cytosine–adenine repeats, affects the promoter activity. It is suggested that serum IGF1 levels are inversely associated with the length of CA repeats. There are studies reporting that the carriers of the CA 19 allele are more likely to develop some cancer types through chronically high IGF1 levels. The relationship between IGF1 and thyroid cancer derived from the experiences in acromegalic patients as thyroid cancer freguency was found to be increased in acromegaly patients. The aim of our study was to examine CA 19 allele frequency in thyroid cancer patients and healthy controls and determine the association of this polymorphism with thyroid cancer and with its prognostic factors.
Patients and methods
161 patients with well differentiated thyroid cancer (papillary and follicular) were included in this study. The clinicopathological variables and prognostic factors were obtained from the medical records. Age and sex matched 101 volunteers were accepted as control group. The IGF1 (CA) repeats were studied with PCR by using proper primers belonging to IGFI (CA) 19 area from DNA samples in both groups.
Results
The frquency of CA 19 allele was not different in thyroid cancer patients than the control group ($P=0.87$). But within the thyroid cancer patients CA 19 allele was found to be associated with soft tissue and vascular invasion (P values were 0.03 and 0.05 respectively).
Conclusion
IGF1 gene polymorphism (CA 19 allele) is found not to be associated with the development of thyroid cancer but it is found to be associated with some poor prognostic factors like soft tissue and vascular invasion in well differentiated thyroid cancer patients.

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P594

Comparison of elastography and conventional ultrasonography in the diagnostics of thyroid nodules, elastographic features of follicular lesions of undetermined significance

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Background
Elastography is a procedure that widen diagnostic ultrasonography (US) but its significance in thyroid diagnostics has not been settled.
Aim
Comparison of usefulness of elastography and conventional malignancy risk features (MRF) in the diagnostics of thyroid nodules, analysis of elastographic characteristics of follicular lesions of undetermined significance (FLUS).
Methods
Analysis included 38 benign lesions (BL), 15 malignant neoplasms (MN) and 67 FLUS. MRF (according to current recommendations), elastography score (ES) based on 4-grade scale of tissue stiffness and strain ratio (SR) of examined lesion and surrounding tissue were evaluated.
Results
MN more often than BL showed MRF>1 (66.7 vs 34.2%; $P<0.05$). Suspicious elastogram (ES>2) was observed in MN more often than in BL (65.5 vs 32.0; $P<0.005$). Relative risk (RR) of malignancy rose when SR>2 (RR$=9$; $P<0.001$); SR>2 was observed in MN more frequently than in BL (66.7 vs 29.7%; $P<0.01$). Moderate positive correlation between SR and ES was found ($r=0.58$; $P<0.05$), as well as low positive correlation between ES>2 and MRF>1 (tau b$=0.28$; $P<0.05$). MRF>1, ES>2, SR>2 sensitivity were similar (66.7; 65.5; 66.7% respectively). Combining both elastography parameters (ES>2 or SR>2) increased sensitivity of the elastography to 91.7%, specificity 51.4%. Adding MRF>1 feature did not significantly improve sensitivity (92.3%) yet it decreased specificity (34.3%). Using single elastography parameter associated with MRF>1 feature was also less effective (SR or MRF>1: sensitivity-91.7%, specificity-45.5%; ES or MRF>1: sensitivity-80.0%, specificity-47.4%). FLUS showed similar elastography features to BL (ES>2–27.1%, SR>2–24.8%) while being similar to MN in >1MRF evaluation (62.7%) and different from BL ($P<0.01$).
Conclusions
Sensitivity of single elastography or MRF is similar. Still, combining both ES and SR is more effective than MRF evaluation. Considering 5% malignancy risk in FLUS in our population, FLUS elastography characteristic is more reliable than MRF analysis.

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P595

Preoperative octreotide therapy in acromegaly: associations between effects on glucose homeostasis and biochemical cure

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Objective
In acromegaly, high GH/IGF1 levels are associated with abnormal glucose metabolism. Treatment with somatostatin analogues (SSAs) reduces the GH and IFG-1 levels. However, SSAs may worsen glucose homeostasis despite this, due to concomitant inhibition of insulin secretion. We studied the possible association between biochemical cure and glucose homeostasis in *de novo* patients with acromegaly.
Design
Post hoc analysis from a randomised controlled trial of newly diagnosed acromegalic patients in Norway during 1999–2004.
Methods
55 *de novo* patients with acromegaly not using antidiabetic medication were included, 26 received SSA for 6 months preoperatively. HbA1c and an oral glucose tolerance test (OGTT) were performed at diagnosis, before surgery and 3 months postoperatively. Area under curve of glucose (AUC-G) was calculated. Indices of glucose homeostasis were compared between cured and non-cured patients.
Results
No associations between basal IGF1/GH levels and OGTT, (AUC-G) or HbA1c were found. After SSA treatment, the percentage reduction in both mean GH and IGF1 correlated positively with percentage ($P=0.021$ and $P=0.001$) and absolute ($P=0.0024$ and $P=0.010$) reduction in HbA1c levels. Biochemical cure by IGF1 and nadir GH, or IGF1/nadir GH alone after SSA treatment were also associated with greater absolute reduction in HbA1c levels ($P=0.003$, $P=0.026$ and $P=0.009$ respectively). Three months postoperatively, biochemical cure by IGF1 and nadir GH were associated with reduced (AUC-G) ($P=0.041$).
Conclusions
In *de novo* patients with acromegaly, disease activity did not correlate to glucose homeostasis indices. After SSA treatment, reduction of GH and IGF1 and biochemical cure were associated with reduction in HbA1c. Biochemical cure 3 months postoperatively was associated with lower AUC glucose. Thus, hormonal control of GH and IGF1 was associated with improved glucose homeostasis in patients with acromegaly.

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P596

Pulmonary neuroendocrine tumor presenting with thyroid gland metastasis: a case report

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Introduction
Neuroendocrine tumors (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 tumor (TC), atypical carcinoid tumor (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 years old woman, affected by a cervical anterior tumor 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 goiter with bilaterally lymph nodes enlargement with suspicious malignancy characters. 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, cromogranin A, calcitonin, carcinoembryonic antigen, ACTH, PTH, TSH, FT_4 were normal. Fine needle aspiration biopsy of her left thyroid lobe nodule was performed and the cytopathological exam was compatible with a neuroendocrine tumor metastasis. Thoracic and abdominal computed tomography was normal at that moment. Chest CT revealed the primary pulmonary tumor at 6 months after presentation.
Conclusions
The therapeutic option for advanced or metastatic NETs is mainly palliation of symptoms; options need to be individualized and, therefore, rely on the knowledge of multidisciplinary teams.
Key words
Pulmonary neuroendocrine tumor, small cell lung carcinoma, thyroid metastasis.
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P597

Everolimus in monotherapy as a therapeutic option in paragangliomas/pheochromocytomas

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Introduction
Everolimus is a drug selective inhibitor of mTOR. In 2012 a Phase 2 study* of everolimus monotherapy demonstrated modest efficacy in patients with pheochromocytomas/paragangliomas. Our objective was to evaluate the efficacy and safety of everolimus in a patient with paraganglioma. (*Phase 2 study of everolimus monotherapy in patient with nonfunctioning neuroendocrine tumor or pheochromocytomas/paraglangliomas. Do-Young Oh *et al*. *Cancer* 2012 **15** 6162–6170).
Clinical case
We present a 29 years old man with recent arterial hypertension diagnosis (triple therapy), vomiting, and weight loss. A scan study shows left para-aortic retroperitoneal mass of 7.4×8.5×8 cm involving the celiac trunk, superior mesenteric artery and left renal hilum. The cytology result by endoscopic ultrasound was spindle cell tumor, suspected of gastrointestinal stroma tumor (GIST). The pathological diagnosis after biopsy exploratory laparotomy was infiltration by paraganglioma. A metaiodobenzylguanidine scintigraphy show patholocical uptake in retroperitoneal mass, 9th right rib and left iliac bone, with great elevation of urinary catecholamines (normetanephrine: 12.832 μg/24 h; dopamine: 1.345 μU/24 h). The patient was treated with ^{131}I-MIBG, 200 mCi by i.v. infusion. A CT control showing progression of disease with high catecholamines (normetanephrine: 18.140 μg/24 h; dopamine: 1.944 μU/24 h). We tried treatment with cyclophosphamide, vincristine and dacarbazine (CVD) in cycles every 21 days with a partial response by CT and biochemical monitoring (normetanephrine: 11.325 μg/24 h; dopamine: 830 μU/24 h). However the treatment was suspended after the second cycle for severe toxicity (ventricular systolic dysfunction severe, hepatolisis, neutropenia, anemia, thrombocytopenia and refractory hypertension). In this moment we started treatment with everolimus (10 mg/24 h). After ten treatment cycles the disease has remained stable (normetanephrine: 8.706 μg/24 h; dopamine: 737 μU/24 h) with good blood pressure control and improvement of pain. No important side effects were observed.
Conclusions
In cases of pheochromocytomas/paragangliomas with severe toxicity after treatment by chemotherapy CVD, everolimus in monotherapy keep the response with good tolerance, so it may be a good treatment option in this cases.
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P598

Expression of somatostatin and dopamine receptors in neuroendocrine tumors: correlation of immunohistochemical findings with somatostatin receptor scintigraphy visual scores

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Background
The expression and/or co-expression of somatostatin (sstr1–5) and dopamine (DR) receptors in neuroendocrine tumors (NETS) is of clinical interest as their expression implies that NETS could be treated with combined targeted therapy. In addition, the expression of sstrs permits tumour visualization with radiolabelled sst analogs (^{111}In-DTPA-OctreoScan).
Methods
We analyzed preoperative Octreoscans findings (also graded for the radioligand uptake as visual score) of 96 patients (53 males) with NETS and compared them with their immunohistochemical (IHC) reactivity for sstr2, sstr3, sstr5 in all samples and D2R in a subset of patients. The findings of both methods were compared.
Results
70 patients had gastrointestinal (GI)-NETS and 26 lung NETS. In 67/96 cases (69.8%) there was concordance of the IHC (all sstr2 positive) with the findings of the Octreoscan ($P<0.001$), while in 17.8% cases positive ICH was seen along with negative Octreoscan and in 12.5% positive octreoscan was seen along with negative IHC. In 60 cases (62.5%) sstr2 was expressed and in lesser rates sstr3 and sstr5 (29.5 and 20.8% respectively). In GI-NETS, the concordance between the two methods decreased in 45/70 (64.3%) ($P=0.25$) while in lung NETS increased in 22/26 (84.6%) ($P=0.003$). Octreoscan score had a high positive correlation with sstr2 ($r=0.6$, $P<0.001$), sstr3 ($r=0.4$, $P<0.001$) and D2R ($r=0.5$, $P=0.01$) expression, while sstr2 expression was positively correlated with sstr3 ($r=0.6$, $P<0.001$) and sstr5 ($r=0.5$, $P<0.001$) and between sstr3 and sstr5 ($r=0.5$, $P<0.001$). Sstr2 expression was positively related to D2R only in small sized tumors (<2 cm) ($r=0.8$, $P=0.001$) while in large sized tumours octreoscan score was no more related to D2R expression. Tumour diameter and sstr2 IHC were the only parameters that could predict the positivity of octreoscan in the multivariate logistic analysis ($P=0.001$, OR: 1.061, CI: 1.024–1.098 and $P=0.011$, OR: 5.502, CI: 1.482–20.424 respectively).
Conclusions
Both methods, IHC expression of sstrs and Octreoscan are of great importance and they complement each other. The expression of DR2 in such tumours is of potential clinical significance.
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P599

Analysis of allelic imbalance frequency in 10q region covering PAPSS2 and PTEN loci in follicular cell-derived thyroid tumours

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Genetic instability, i.e. loss of heterozygosity (LOH) and microsatellite instability (MSI) represent molecular disorders acquired by the cell during neoplastic transformation. Genetic instability is a frequent molecular event in thyroid pathogenesis, found at the early and the late stages of thyroid tumorigenesis. In thyroid neoplasms genetic instability was found in many chromosomal regions and is observed especially in cell-derived thyroid tumours. Alterations in PTEN loci were previously detected in hereditary form of follicular thyroid cancer. In this study we focused on to the following chromosomal regions: 10q23.2, 10q.23.31, 10q24–24.1 – the loci of *MMRN2*, *KIF11*, *PAPSS2* and *PTEN* genes.
Aim of the study
An attempt to answer the question whether the presence of LOH/MSI in 10q in thyroid carcinomas can be regarded as diagnostic marker.
To analyze the potential role of LOH/MSI in 10q involved in follicular cell-derived thyroid pathogenesis – were performed PCRs using four microsatellite markers (D10S1687, D10S583, D10S215, D10S541). The study included a group of 93 patients with initial diagnosis of 'follicular neoplasm' in FNAB, afterwards verified as benign (FA), malignant thyroid lesions (PTC, FTC) or nodular goitres (NG).
The LOH/MSI analysis was conducted using allelotyping method on 3130 xl Genetic Analyzer (Applied Biosystems, Hitachi) and the allele detection was assessed using GeneMapper Software v 4.0.
The highest genetic instability was detected in *PAPSS2 locus* (10q24; D10S215 marker) – with the frequency – 22%, and the lowest in KIF11 *locus* (10q24.1; D10S583). LOH/MSI was detected for any of four markers in 26 from 93 patients (28%), with the higher frequency for FTC and FA group. In FTC group, the most frequent genetic instability (LOH/MSI) was observed for D10S215 in *PAPSS2 locus*, in FA group for D10S541 in PTEN *locus*. In PTC specimens LOH/MSI was detected mainly for D10S1687 marker in MMRN2 *locus*.
The obtained data confirmed the presence of LOH/MSI in 10q in the early and late stage of thyroid cancerogenesis. The different frequency of LOH/MSI occurrence in analysed *loci* may be considered as potential marker differentiating the PTC from FA and FTC.

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P600

Cushing's syndrome caused by ectopic corticotrophin secretion

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Cushing's syndrome caused by ectopic ACTH secretion (EAS) constitutes ~10% of Cushing's syndrome (CS).
The aim of this study was to present experience of our Clinic with EAS.).
Patients
Twelve patients, aged 14–70 years: four females and eight males.
Outcomes and measurements
Clinical features, medical examination, morning electrolytes, glucose level, serum cortisol, ACTH levels, midnight plasma cortisol concentration and dexamethasone suppression tests. Imaging tests: computed tomography (CT), somatostatin receptor scintigraphy (SRS), magnetic resonance imaging, positron emission tomography and histopathological examinations.
Results
Seven patients were diagnosed as NEN, one patient as medullary thyroid carcinoma (MTC), one patient as pheochromocytoma, one patient as ovarian carcinoma, one patient as lung carcinoma and one as esthesioneuroblastoma.
Clinical features, like those in CS: central obesity, signs of hypercatabolism, bruising and severe amyotrophy with or without facial fullness or weight gain, severe hypokalemia, life-threatening infections, muscular weakness and psychiatric disorders were present in almost all patients. Flush or diarrhea were observed in patients with MTC and with metastatic carcinoid tumors.
Enlarged adrenal glands were detected in CT scans in all patients. SRS was positive in all patients with NET and carcinoids.
Because of severe condition and complications each patient required individual treatment.
Ten patients died, eight due to metastases and two due to metabolic complications.
Conclusion
i) Localization of the ACTH-secreting tumor is often difficult to dicover and may require multiple modalities.
ii) Surgical resection of the source of ACTH production may be curative in cases of benign neoplasms.
iii) Metastatic tumors as well as metabolic complication of hypercortisolemia can be the reason of patient's death.

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P601

Expression of proliferating markers: PCNA and Cdk1 in hyperplastic lesions of the parathyroid glands

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Background
Proliferating cell nuclear antigen (PCNA) is a cell cycle marker protein. It interacts with more than 100 proteins involved in DNA replication, DNA repair, cell cycle control, chromatin remodeling/epigenetic inheritance, chromatid cohesion and transcription. Cyclin-dependent kinase 1 (Cdk1) is a serine/threonine protein kinase which regulates diverse cell cycle transitions (G1/S, S and G2/M phases) and associates with different cell-cycle stage-specific cyclins. Both of these proteins could be potentially useful in diagnosis of primary hyperparathyroidism which is one of the most common endocrine disorders caused by adenoma (80%), hyperplasia (15%) and carcinoma (5%).
Aim
The aim of the study was to assess the immunohistochemical expression of PCNA and Cdk1 as a potentially useful in diagnosis of hyperplastic lesions of the parathyroid glands.
Methods
For immunohistochemistry, parathyroid specimens of patients undertaken surgery due to primary hyperparathyroidism caused by adenoma and primary hyperplasia were investigated. Frozen sections were incubated with purified mouse monoclonal antihuman antibodies: anti-PCNA (clone 24/PCNA) and anti-Cdk1 (clone 1/Cdk1/Cdc2) from BD Biosciences. The immunohistological investigations were performed by the BrightVision method from ImmunoLogic. The number of proliferating cells were counted and expressed as a mean value of at least six counted high power fields (HPF, ×400). The sections were counterstained with Mayer's haematoxylin.
Results
Positive Cdk1 immunoreaction was significantly increased in parathyroid adenomas, whereas PCNA was considerably lower in adenomas and hyperplasias compared to healthy parathyroid glands. Positively stained cells were localized in the well vascularized region of the parathyroid nodule.
Conclusion
Numerous different mechanisms are responsible for hyperplastic changes: activation of oncogenes, inactivation of tumor-suppressor genes, epigenetic changes and disturbance of the balance between growth factors and other transmitter substances including proteins involved in cell cycle regulation.

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P602

Immunohistochemical assessment of parafibromin in primary hyperparathyroidism

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Background
Parafibromin is an ubiquitously expressed protein and a member of the polymerase-associated factor 1 complex associated with RNA polymerase II,

which regulates transcription elongation, histone modification and cell proliferation. It is encoded by the *CDC73* gene also known as the *HRPT2* gene. Endogenous parafibromin inhibits expression of *MYC* gene that encodes the c-Myc proto-oncogene. Parafibromin has three nuclear localization signals, and mutation of this region blocks nuclear targeting. Overexpression of WT can induce apoptosis in transfected cells. The pathological distinction between parathyroid neoplasms and hyperplasias remains difficult in several cases. Parafibromin can be useful in differential diagnosis of parathyroid carcinoma from adenoma and may be a prognostic marker.
Aim
The aim of the study was to examine whether immunohistochemical expression of parafibromin may be useful in distinguishing between parathyroid hyperplasia and neoplasia.
Methods
Tissue specimens were taken from patients with primary hyperparathyroidism due to adenoma, hyperplasia and carcinoma. Normal glands served as controls. In a standard immunohistochemical procedure, MABs to parafibromin from Santa Cruz Biotechnology were applied. The dilution of the primary antibodies was 1:500 and was verified in a series of pilot experiments. The immunohistological investigations were performed by the BrightVision method from ImmunoLogic. The sections were counterstained with Mayer's haematoxylin.
Results
Parafibromin was underexpressed in parathyroid carcinoma compared to adenoma, whereas the amount of positively-stained cells in adenoma was lower than in healthy parathyroid tissue.
Conclusion
Parafibromin can be useful in differential diagnosis of parathyroid carcinoma, adenoma and hyperplasia, and may be a prognostic marker.

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P603

Apoptotic cell index in non-neoplastic lesions of the parathyroid glands

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Background
Primary hyperparathyroidism is one of the most common endocrine disorders caused by adenoma (80%), hyperplasia (15%) and carcinoma (5%). It is often difficult to differentiate between hyperplasia from an adenoma of a parathyroid gland. Accordingly, the aim of this study was to assess apoptotic index as a potentially useful in diagnosis.
Methods
Apoptotic cells was investigated in the parathyroid specimens of 21patients (4M, 17F, average age of 57 years) undertaken surgery due to primary hyperparathyroidism caused by adenoma, $n=11$, and primary hyperplasia, $n=10$ cases. For immunohistochemistry, frozen sections were incubated with murine monoclonal antihuman antibodies, anti-CD253 and anti-CD95. The dilution of the primary antibodies was verified in a series of pilot experiments. The immunohistological investigations were performed by the EnVision method with New Fuchsine Chromogen from DAKO. The number of apoptotic cells (apoptotic index) were counted and expressed as a mean value of at least six counted high power fields (HPF, $\times 400$). The sections were counterstained with Mayer's haematoxylin. The protocol was approved by the Institutional Ethics Committee.
Results
Unexpectedly, the apoptotic index was the highest in capillary endothelial vessels stained both with CD253 and CD95 in all cases. Only a few chief cells were positively stained with these antigens. There were no differences between adenoma and primary hyperplasia in the relation to number of apoptotic cells.
Conclusion
The results suggest that increased apoptotic capillary endothelial cells may be related to pathogenesis of hyperplasic state of the parathyroid glands.

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P604

Neuroendocrine cancer of the ampulla of Vater: clinical course in seven patients: material of Department of Endocrinology in Szczecin, Poland

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Introduction
Neuroendocrine cancer of the ampulla of Vater area belongs to the most rare GEP-neuroendocrine tumors (NET). In the literature, there are few reports of extremely malignant course of this cancer. Among 242 patients with NET from the Department of Endocrinology in 2009–2013, 58 pancreatic NET were discovered, among which seven patients had neuroendocrine cancer of the ampulla of Vater. The aim of this study was to determine the clinical characteristics, staging, grading and survival rate in patients with such neuroendocrine carcinoma.
Materials/designs
Seven patients were evaluated (5F/2M) aged from 41 to 75 years (mean 58 ± 11.5). The average age of diagnosis was 63 ± 7.4 years.
Results
The most common clinical symptoms were unspecific abdominal pain and jaundice. The average value of Ki67 index was 44.7% (21–82%). Clinical stage was T1M1N0 in three patients, T2M1N0 in two patients and T2M1N1 in two patients. The average concentration of chromogranin A was 138 ± 13.5 ng/ml, with no correlation with the clinical stage of the tumor. All patients had high expression of somatostatin receptors in somatostatin receptor scintigraphy (SRS) and ^{68}Ga-labeled DOTA-TATE PET. The primary focal lesion was revealed in the ampulla of Vater area in the EUS examination with the size range 1.8–3.5 cm (mean 2.4 cm). In three patients that underwent total surgery there was no recurrence of the cancer for 3 years. Four patients did not qualify for radical surgery and therefore underwent chemotherapy with subsequent somatostatin analogues treatment. Next two patients underwent radionuclide treatment due to progression of the disease. The current median survival of these patients is 3.2 ± 0.7 years.
Conclusion
Patients with neuroendocrine carcinoma of the ampulla of Vater demonstrate a high degree of staging and histopathological grading system with scanty and late occurring symptoms. They require long-term treatment and monitoring.

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P605

'Noninsulinoma pancreatogenous hypoglycemia syndrome'; a case report of adult nesidioblastosis from Turkey

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The most common reason for the rare condition of hyperinsulinemia-related hypoglycaemia is insulinoma, a tumor of pancreatic islet cells. However, nesidioblastosis characterized by diffuse or focal hyperplasia of the pancreatic islet cells is the most common cause of hyperinsulinemic hypoglycemia in newborns. Nesidioblastosis seen in newborns is now called 'persistent hyperinsulinemic hypoglycemia of infancy' (PHHI) while the condition in adults is called 'noninsulinoma pancreatogenous hypoglycemia syndrome' (NIPHS) as a separate entity. It is impossible to clinically differentiate insulinomas from NIPHS.
A 38-year-old female presented with neuroglycopenic symptoms in the form of drowsiness, inability to speak, numbness in the mouth, and nausea in the last 3–4 months. Endogenous hyperinsulinemia was found with recurrent neuroglycopenic symptoms (the glucose level was 25 mg/dl, insulin 43.9 μ/ml, and C-peptide 5.54 ng/ml). No lesion was found on imaging tests including enhanced computed tomography (CT) methods performed with a preliminary diagnosis of insulinoma. A suspicious hyperperfusion was present in the pancreatic tail on the perfusion CT examination performed after obtaining approval. The selective arterial calcium stimulation test (SACST) result was consistent with a diffuse disease in the body and tail. The patient underwent partial (75%) pancreatectomy and is now followed up as a diabetes patient on intensive insulin treatment at the postoperative 38th month.

The NIPHS is rarely seen in the adult age group. SACST seems to be the most suitable test to differentiate diffuse or multiple disease from insulinoma and to guide the surgery when advanced radiological imaging methods are inadequate to detect the presence of insulinoma. Regarding perfusion CT, it would be more appropriate to wait for comparative data to be put forward in a more consistent manner. When no response to medical treatment, partial/total pancreatectomy is appropriate treatment option as it enables recovery from the hypoglycemic episodes despite leading to diabetes.

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P606

Breast metastasis from medullary thyroid carcinoma in a man

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Introduction
Medullary thyroid carcinoma (MTC) originated from parafollicular C cells of the thyroid gland is a rare histological type of malignancy. Common sites of metastases are liver, lungs and bones, while metastases in other sites are extremely rare. Breast metastases from MTC are reported in 20 cases, and only in women.
Case report
A 67-year-old man was presented after thyroidectomy for further evaluation and treatment. Histology was positive for MTC with extrathyroidal extension and bilateral cervical lymph node metastases. Postoperative calcitonin was 613.6 pg/ml (normal range <10 pg/ml) and RET protooncogene was found negative for multiple endocrine neoplasia. Computed tomography and bone scan revealed metastases to lung and bone. Administration of tyrosine kinase inhibitor (vandetanib) was decided which was soon stopped due to serious adverse events (thrombocytopenia, bleeding, and impaired renal function). Antimotility agents and somatostatin analogues (octreotide LAR 20 mg) were used to control diarrhea. Seven months later he presented a painful swelling of right breast. Breast ultrasound revealed the presence of multiple, solid masses in the right breast and mammography was suspicious of malignancy. Core needle biopsy was positive for metastases from the known MTC. Palliative external beam irradiation was decided with mild relief of pain. The patient succumbed 1 month later. A literature search was conducted. No other cases of breast metastases from MTC in men were found.
Conclusion
This is the first reported case of breast metastasis from MTC in men. Breast masses in the course of MTC should be evaluated for metastases since the therapeutic approach is different from that of primary breast carcinoma. Palliative external radiation therapy should be considered for metastatic and lesion causing pain.

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P607

A rapid thymic carcinoma in a patient with multiple endocrine neoplasia type 1

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Introduction
Thymic neuroendocrine (NE) tumors associated with multiple endocrine neoplasia type 1 (MEN1) are rare, variably documented in 1–8% cases. They are malignant and aggressive tumors and form a major cause of mortality in MEN1.
We report a case of thymic NE carcinoma developing rapidly after parathyroidectomy in a MEN1 patient.
Case
A 45 years old man was allowed for headaches, the biology showed a hypercalcemia, a hypophosphoraemia and high PTH. The imaging revealed polar parathyroidal adenoma with hypophyseal adenoma with rates of prolactinemia $=1768$ mU/ml. The abdominal MRI–Pet Scan–DG and the scintigraphy in the ocréotide allowed to bring to light a metabolic activity of the mass of the thymic cavity with a necrotic and atypical aspect without distant metastases, five pancreatic nodules and bilateral adrenal nodules without arguments in favour of a pheochromocytoma. The patient has benefited from the resection of a retro-tracheal parathyroidal adenoma, from a malignant thymoma of type invasive P3 the pericardium and the mediastinal fat completed by a mediastinalradiotherapy and hypophyseal adenomectomy.
The search of MEN 1 showed itself positive.
Conclusion
Thymic NE tumors in MEN1 are commoner in males and smokers and are almost always hormonally inactive and diagnosed incidentally.They are malignant, aggressive tumors and are widely invasive and metastatic at presentation (usually to bone). They are never the presenting feature of MEN1 and almost always occur after hyperparathyroidism, providing an opportunity for prophylaxis for these tumors at the time of parathyroid surgery.
Thymic NE tumors present later, usually 15–20 years after. In contrast, our patient had a rapid presentation of thymic NE carcinoma.
Conclusion
These two case reports illustrate the interest of a fine analysis of the usual clinical and biological data as well as the contribution of the current techniques of biology and imaging for the etiologic and topographic diagnosis of hormonal hypersecretions of which some are as here, very exceptional.

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P608

Metastatic bone disease in patients with neuroendocrine tumors

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Objective
The prevalence of metastatic bone disease in patients with neuroendocrine tumours (NETs) and their response to first line treatment with biphosphonates.
Methods
We studied 271 patients (141 females) with NETs: 54 gastric, nine duodenal, 102 pancreatic, 29 small intestine, 29 appendix, 14 colon, 15 lung, one thymic, 20 unknown primary and ten elsewhere. Since September 2012 all patients with NETs and bone metastases were recruited to receive 4 mg of zoledronic acid monthly for two consecutive years. They were all followed-up by biochemical parameters and bone scan.
Results
In the whole cohort 13 (7.6%) patients had bone metastases. The prevalence of bone disease was 4.9% in pancreatic (five patients), 3.4% in small intestine (one patient), 7.1% in colon (one patient), 20% in lung (three patients), 100% in thymic NETs (one patient), and 10% in NETs with unknown primary NET (two patients). Two hundred 50 patients had sporadic NETS and 21 in the context of MEN1 and VHL; only one patient with MEN1 (4.8%) had bone disease. Ten patients were recruited in the treatment arm, three with lung (one completed 1 year of follow-up with improvement), three with pancreatic (one died after the 1st month of treatment), one with thymic (died before the 6-month evaluation) and one with sigmoid NET and two with unknown primary lesion (one died before a 6-month evaluation and the other had deterioration).
Conclusion
Approximately 4.2% of patients with NETs present bone disease. Our preliminary results show a 50% of positive response after treatment with biphosphonates in patients who remain alive during treatment.

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P609

Adrenocortical carcinomas: retrospective analysis of the last 22 years

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Introduction
Adrenocortical carcinoma (ACC) is a rare disease, with a severely adverse prognosis. Clinical reports, even when including a limited number of cases, can

contribute to its knowledge. This study aims to characterize patients followed at our department between 1991 and 2013.
Methods
Retrospective analysis of the clinical records of patients with pathological confirmation of ACC. Statistical analysis: SPSS21.
Results
22 patients (2♂/20♀), 44.5±19.3 years at diagnosis were included. At presentation: abdominal pain (40.8%, $n=9$), signs of hypercortisolism (31.7%, $n=7$), asymptomatic (9.1%, $n=3$). Laboratory: UFC elevation (50%, $n=11$), testosterone (18.2%, $n=4$) and S-DHEA (9.1%, $n=2$). Radiologically: six patients presented invasiveness: kidney (2), diaphragm (2), inferior cava vein (ICV)+kidney (1), ICV+diafragm (1); and eight metastasis: limphatics (4), hepatic (3) and hepatic+lymphatics+pulmonar (1). Twenty were operated: described as complete resection in 90% of the cases; mean tumor weight 740± 643 g. Staging (ENSAT): stage II–1 one patients; III–four patients and IV–five patients. Histopathology: incomplete total characterization (median Weiss score ≥ 3). During follow-up, eight patients presented local recurrence, and 12 new metastasis – lungs (10), liver (5), lymphatics (5) and bone (2). 14 patients were treated with mitotane, in 64.3% ($n=9$) of the cases after recurrence (initial dose: 2.8±1.8 g/day; maximum dose: 5.6±3.1 g/day and median cumulative dose: 531.5 g, during a median of 9.5 months). The mitotanemia was evaluated in ten patients: 70% ($n=7$) achieved therapeutic levels. Comparing patients at same stage, those treated with mitotane presented longer survival. One patient had chemotherapy (EDP) associated to mitotane. Median global survival was 11 months (0–257 months), slightly higher in younger adult patients with non-functioning tumors. Seven patients still alive, four of them in remission.
Conclusion
As had been shown in multiple studies of patients with ACC, the best chance of survival may be achieved by an early detection and complete surgical resection of the tumor. Despite the global poor prognosis, we emphasize the long survival of some patients. Although this remains controversial, in this series younger adult age at diagnosis, presence of non-functioning tumor and treatment with mitotane, seems to have allowed some increased survival.

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P610

The value of parathyroid hormone determination in ultrasound-guided fine-needle aspirates (FNA–PTH) for preoperative localization of parathyroid lesions.

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Introduction
Ultrasound imagining of parathyroid lesions is often challenging, as they may be difficult to distinguish from thyroid lesions or enlarged lymph nodes.
Aim
The aim of the study was to assess the value of parathyroid hormone determination in ultrasound-guided fine-needle aspirates-(FNA) in preoperative localization of parathyroid lesions.
Materials and methods
We measured FNA–PTH in 30 consecutive patients with primary hyperparathyroidism referred to our department and qualified for surgery from January 2012 to December 2013. All patients underwent neck ultrasound and biopsy specimens of suspicious lesions were taken by the same physician, blinded to other localization studies results (MIBI scans and CT scans). A positive cutoff value for PTH washout concentration was defined as superior to serum PTH level obtained at the same time.
Results
According to histological examination, elevated FNA–PTH concentration correctly identified all but one parathyroid lesions. Combined ultrasound-FNA–PTH was more specific than combined ultrasound-MIBI scan in identifying parathyroid lesions.
Conclusion
Measurement of FNA–PTH concentration is useful tool for identifying parathyroid gland lesions, especially in patients with concomitant nodular goiter.

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P611

TSH suppressive therapy accelerates progression of sacropenia in post-menopausal women

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Background
TSH-suppressive therapy in patients with differentiated thyroid carcinoma (DTC) leads to iatrogenic thyrotoxicosis and may be associated with alterations in body composition and bone mineral density (BMD). Its effects on a sarcopenia in elderly have not been in detail investigated.
Objective
The objective was to compare changes in total and areal lean body mass (LBM), body fat mass (BFM) and BMD in postmenopausal female patients with DTC during the first 5 years of TSH-suppressive therapy and in control subjects.
Subjects and methods
One hundred and forty females with DTC (menopausal <10 years ($n=83$) or >10 years ($n=57$)) and 40 control subjects (menopausal <10 years ($n=15$) or >10 years ($n=25$)) were included in this retrospective study. Body composition and BMD were measured at 1, 3 and 5 years after initiation of TSH suppressive therapy.
Results
Body composition and BMD were not significantly different at baseline between the study groups. At 5 years, the results showed that women with DTC more than 10 years post menopause have a significantly increased loss of total LBM and leg LBM ($P=0.02$ and $P=0.03$) and total BFM ($P=0.04$).
Conclusion
Lean mass decreases to a greater extent in women with DTC more than 10 years post menopause suggesting that TSH-suppressive therapy may accelerate progression of age-related muscle loss in post-menopausal women.

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P612

Metabolic and cardiovascular complications in patients with adrenal incidentalomas

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Introduction
We evaluated the prevalence of metabolic and cardiovascular complications in a Romanian population with adrenal incidentalomas in comparison with an age-matched control group, evaluated in our clinic.
Patients and methods
After excluding patients with overt functioning adrenal tumors, subclinical pheochromocytomas, malignant tumors, myelolipomas, data were retrieved from the files of 190 patients with adrenal incidentalomas ≥ 1 cm and 85 age-matched control patients (C) evaluated for non-functioning thyroid nodules or osteoporosis. According to the current consensus of evaluation, ten patients (5.2%) were diagnosed with subclinical Cushing's disease (SCS) and 180 patients with non-functioning adrenal tumors (NFAT).
Results in groups SCS, NFAT and C. Mean age was similar (56, 55 and 52.5 years), with a female predominance; prevalence of obesity and overweight was 75, 74 and 49%, higher in NFAT vs C ($P<0.001$); prevalence of hypertension was 70, 56 and 40%, higher in NFAT vs C ($P<0.05$) and borderline higher in SCS vs NFAT ($P=0.05$); prevalence of glucose abnormalities (diabetes mellitus, impaired fasting glucose or glucose tolerance) was 50, 30 and 9%, higher in SCS vs NFAT, in SCS vs C and in NFAT vs C ($P<0.01$ in all comparisons); prevalence of dyslipidemia was 100, 76 and 39%, higher in SCS vs NFAT ($P<0.001$) and in SCS vs C ($P< 0.01$); prevalence of ischemic heart diseases was 50, 22 and 12%, higher in SCS vs NFAT ($P<0.001$), in SCS vs C ($P<0.01$) and borderline higher in NFAT vs C ($P=0.06$); prevalence of stroke was 20, 16 and 1%, higher in SCS AND in NFAT vs C ($P<0.05$ in both comparisons); prevalence of thrombembolism was 0, 1.6, 0%; prevalence of patients with any cardiovascular event was 60, 32 and 14%, higher in SCS and NFAT vs C ($P<0.01$ in both comparisons). Morning serum cortisol, midnight cortisol and morning cortisol after 1 mg overnight dexamethasone suppression test are significantly higher in SCS than NFAT.
Conclusion
Patients with adrenal non-functioning tumors and especially those with subclinical Cushing's syndrome have higher prevalence of risk factors for cardiovascular disease than the age-matched control population.

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P613

Circulating tumor cells in neuroendocrine tumor patients

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Introduction
Neuroendocrine tumors (NET) are heterogenous tumors with variable survival and the frequently occurring ability to metastasize. A basis for metastasis of tumors is invasive growth. One factor participating in this process is the existence of the so called 'circulating tumor cells' (CTC) in the peripheral blood. Up to now there is only rare data available regarding the number of CTCs in NET patients.
Methods
EpCAM protein expression was evaluated in cancer cell lines as well as NET patients. NET patients' peripheral blood mononuclear cells (PBMCs) were investigated by immunohistochemical staining, defining CTCs to be CD45 negative and EpCAM positive. Up to now 14 NET patients were included into the ongoing study (six females, mean age: 48 years (range, 25–80 years); eight males, mean age: 64 years (range, 54–77 years)). The following NETs were included: five pancreatic tumors, three bronchopulmonary tumors, two pheochromocytomas, and four tumors with unknown primary. Eight patients showed morphological detectable metastatic spread (57%).
Results
Analyses of a medullary thyroid carcinoma cell line (TT-cells) showed a stronger EpCAM expression compared to a leukemia cell line (K 562 cells). CTC analyses of NET patient revealed CTC existence within the peripheral blood of 3 (21%) NET-patients (mean number of CTCs: 5/7.5 ml blood). This was the case in one pancreas NET patient, one pheochromocytoma patient, and in one NET patient with CUP (cancer of unknown primary) syndrome. All three patients showed metastatic spread. Correlation analyses between CTC levels and serum chromogranin A levels as well as disease progression are ongoing.
Conclusion
This study underlines the previously described EpCAM expression of NET-cells. Our systematic analysis indicates a correlation between the presence of CTC within the peripheral blood and metastatic spread. Further investigation is needed to underline our results. This study is ongoing.

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Female reproduction

P614

Tissue glucose utilization in the different phenotypes of PCOS women

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We already know that woman with PCOS face increased risk of glucose intolerance, diabetes, metabolic syndrome and cardiovascular disease. However, it seems that it doesn't apply to all women with PCOS and depends on their phenotypes.
Aim of the study
Evaluation of tissue glucose utilization and lipid's profile in different PCOS phenotypes.
Materials and Methods
69 PCOS women were divided into ten phenotypes groups, according to R. Azziz classification based on four characteristics: oligoovulatio, ovaries PCO in USG, separately hirsutism and hyperandrogenemia.
Lab tests were done using ELISA commercial kits. Evaluation methods of insulin resistance used: hyperinsulinemic euglycemic clamp, HOMA–IR, glucose and insulin was measured during OGTT.
Results
Out of 69 PCOS women 22 women belong to the classic phenotype one with oligoovulatio, PCO ovaries, hyperandrogenemia and hirsutism and 18 women with oligoovulatio, PCO ovaries, and hirsutism but without hyperandrogenemia to phenotype five.
The correlation between tissue glucose utilization and BMI, then with FAI is statistically significant.
Allocation of PCOS patients to ten phenotypes doesn't form any separate clusters. However 88% women with phenotype two and 86% with phenotype five, respectively, appeared in two clusters confirming the difference between these phenotypes.
Tissue glucose utilization in PCOS patients is negatively correlated with HOMA and positively with HDL and HOMA but negatively correlated with HDL.
Conclusion
i) Tissue glucose utilization value remains below norm in PCOS patients with hyperandrogenemia suggesting they are insulin resistance and is proper in PCOS patients with hirsutism only suggesting that they are't insulin resistance.
ii) Patients with PCOS, depending on their phenotype, should be considered as two separate groups in terms of their future disease risks. Women without hyperandrogenemia but only with hirsutism don't show any metabolic abnormalities while women with PCOS and hyperandrogenemia show lower insulin sensitivity and abnormal lipid's profile.

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P615

Post load glucose and 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 and type 2 diabetes mellitus (T2DM). The aim of this study was to detect insulin resistance parameters that could be the best predictor T2DM in PCOS when compared with healthy women.
Methods
This study include 114 PCOS women (BMI: 29.2 ± 0.60 kg/m^2; age: 25.3 ± 0.57 years) and 41 controls (age- and BMI-matched) healthy women (BMI $= 28.5 \pm 1.35$ kg/m^2; age: 26.5 ± 0.89 years). In all women OGTT (75 g of glucose) and IVGTT (minimal model analyses) were performed. All women have normal fasting glucose and 2 h glucose level under 7.8 mmol/l.
Results
There was no difference between fasting glucose, but glucose at 2 h of OGTT were still higher in PCOS ($P < 0.05$). Fasting insulin was significantly higher in PCOS (17.02 ± 1.07 vs 12.84 ± 1.72) as well as insulin at the end of OGTT (86.85 ± 7.1 vs 56.31 ± 10.57). There was no statistically significant difference between integrated areas under insulin curve (AUCI) between two groups (10441.12 ± 730.14 vs 8088.36 ± 1078.2). Minimal model analyze confirmed no difference in IV glucose tolerance (kg) between PCOS and controls, as well as in acute insulin response (AIR). Si parameter of insulin sensitivity was significantly lower in PCOS (2.44 ± 0.16 vs 3.51 ± 0.35). Disposition index (AIR $\times$ Si) were significantly higher in controls (166.57 ± 13.9 vs 220.89 ± 33.47). In order to provide accurate and more simple parameters to detect women with PCOS who have IR, we compare standard parameters (fasting or during OGTT) with Si. The best correlation with Si showed OGIS (0.490, $P < 0.01$) obtained from values: glucose from 0, 90, and 120 min and insulin at 0.90 min. Significant but weaker correlation showed HOMA index (0.271, $P < 0.01$) and fasting insulin (-0.247, $P < 0.01$).
Conclusions
These insulin sensitivity indexes could be potentially used to identify subgroups of insulin resistant women with PCOS and at increased risk of T2DM. Our result also suggest that indexes included basal and post load glucose and insulin constitute a more sensitive tool for screening and preventing metabolic abnormalities in PCOS.

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P616

Screening for cushing syndrome in women with hirsutism and oligomenorrhea

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Introduction
Cushing syndrome is a rare etiology of hirsutism and oligomenorrhea.
Objective
Screening for Cushing's syndrome (CS) in patients with hirsutism and oligomenorrhea.
Patients and methods
A prospective study was performed from 2004 to 2012. 210 patients were admitted with the complain of hirsutism and oligomenorrhea. In order to establish

the diagnosis and exclude the CS, all of them were evaluated with overnight dexamethasone suppression test.
Results
CS was excluded for all the patients as they had suppressed cortisol levels following overnight dexamethasone suppression test.
Conclusion
Screening for CS in patients with a diagnosis of hirsutism and oligomenorrhea don't seem to be necessary. Although, it's requiered for patients who have associated clinical sign of hypercortisolism.

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P617

Identification of elevated urine kisspeptin in pregnant women: a novel non-invasive biomarker of placental function?

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Background
Kisspeptin is an RF amide peptide hormone critical for reproductive function. Kisspeptin is also abundantly expressed in the placenta, where it has an important physiological role in regulating placental invasion. Accordingly, plasma kisspeptin levels rise dramatically during normal pregnancy. Lower plasma levels of kisspeptin are associated with poor pregnancy outcomes such as recurrent miscarriage, intrauterine growth restriction and pre-eclampsia. Urinary measurement of kisspeptin may provide a novel and practical tool for screening patients for major obstetric complications. However, it is not currently known whether kisspeptin can be detected and quantified in the urine of pregnant women.
Aim
To determine the clinical utility of urinary kisspeptin measurement in healthy pregnant women.
Methods
49 healthy third trimester pregnant women (gestational age 34 ± 0.6 weeks) from a single maternity unit and 50 healthy non-pregnant women were recruited. Urine and blood were simultaneously collected from all volunteers in plain containers and lithium heparin tubes respectively, each containing 5000 kallikrein inhibitor units of aprotinin. Kisspeptin levels were determined by in-house manual RIA and urine creatinine by kinetic alkaline picrate method.
Results
Mean levels of plasma kisspeptin were over 200-fold greater in third trimester pregnant women compared with non-pregnant women ($13\,783 \pm 864$ pmol/l, pregnant; 65 ± 13 pmol/l, non-pregnant; $P < 0.0001$). Mean levels of urine kisspeptin were greater in pregnant women when compared with non-pregnant women (301 ± 59 pmol/l, pregnant; 80 ± 19 pmol/l, non-pregnant; $P < 0.001$). Urine kisspeptin levels were significantly correlated with plasma kisspeptin levels in pregnant women ($r = 0.35$, $P < 0.01$). The urine kisspeptin:creatinine ratio was also significantly greater in pregnant women compared with non-pregnant (37 ± 6 pmol/μmol, pregnant; 7 ± 1 pmol/μmol, non-pregnant; $P < 0.0001$).
Conclusion
We demonstrate for the first time that kisspeptin levels are elevated in urine during pregnancy. Urine collection may therefore offer a non-invasive and simple method of screening for pregnancy and obstetric complications, which is particularly suited to the busy clinical setting of the obstetric clinic.

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P618

Changes in body composition following 12 months randomized treatment with metformin vs oral contraceptives vs combined treatment in polycystic ovary syndrome

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Background
Central obesity in polycystic ovary syndrome (PCOS) is associated with increased inflammatory markers and increased risk for type 2 diabetes.
Aim
To evaluate the long-term effects of metformin (M) and/or oral contraceptives (OC) on fat mass.
Research design
Randomized, controlled study.
Setting
Outpatient clinic.
Methods
90 patients with PCOS were randomized to 12 months M (2 g/day) or OC (150 mg desogestrel + 30 μg ethinylestradiol) or M + OC. Clinical and hormonal evaluations, oral glucose tolerance tests, and whole-body DXA scans were performed before and after the intervention period.
Main outcome measures
BMI, fat mass measures evaluated by DXA scans.
Results
A total of 65/90 patients completed the study (dropout rates between intervention groups, NS). M and M + OC were superior to OC regarding fat mass, body composition and insulin sensitivity. The median (quartiles) weight changes during 12 months M, OC, and M + OC treatment were −3.0 (−10.3; 0.6), 1.2 (−0.8; 3.0), and −1.9 (−4.9; 0.1) kg, respectively, $P < 0.05$. During multiple regression analyses, changes in body composition during study intervention were predicted by type of medical intervention and not by BMI at study inclusion. Changes in total testosterone were comparable during the three different interventions, but OC and M + OC was superior to M regarding increased SHBG and decreased free testosterone levels.
Conclusions
M treatment is associated with improved body composition compared to OC, whereas OC is associated with decreased testosterone levels. Combined treatment with M + OC should be considered in patients with hyperandrogenism and obesity.

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P619

Serum cocaine and amphetamine-regulated transcript concentrations in women with polycystic ovary syndrome

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Purpose
Cocaine and amphetamine-regulated transcript (CART) influences the appetite, obesity and pancreatic functions. The aim of this study is to determine the CART level of patients with PCOS and examine the relation with the insulin resistance in patients with PCOS.
Methods
41 patients with PCOS and and 39 healthy women were included in the study whose age and BMI matched. For PCOS diagnosis, 2003 Rotterdam criteria were used. The fasting serum glucose, insulin, CART and free testosterone levels of the all participants were measured. HOMA–IR was used in order to calculate the insulin resistance, and QUICKI-IS index was used to measure the insulin sensitivity.
Results
The two groups did not differ much in term of serum glucose concentrations ($P > 0.05$). In patients with PCOS the serum insulin levels (14.11 ± 6.3 vs 12.4 ± 5.1 μU/ml, $P = 0.03$) and HOMA–IR (3.01 ± 1.3 vs 2.61 ± 1.07, $P = 0.015$) were significantly higher; while QUICKI-IS (0.34 ± 0.02 vs 0.33 ± 0.02, $P = 0.031$) and serum CART (90.39 ± 8.45 vs 94.34 ± 11.21 pg/ml, $P = 0.04$) levels were significantly lower. In the correlation analysis performed, there was a significantly positive correlation between CART and QUICKI-IS ($r = 0.173$, $P = 0.049$) and significantly negative correlations between HOMA-IR ($r = -0.274$, $P = 0.002$). In the regression analysis, while the contribution of CART to HOMA-IR was detected.
Conclusions
As a result of our study, CART may be thought to have an impact on the obesity seen in patients with PCOS and their physiopathology.

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P620

Plasma levels of nesfatin-1 in patients with polycystic ovary syndrome

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Introduction
Polycycstic ovary syndrome (PCOS) is an important disorder in women of reproductive age which is characterised with menstrual dysfunction, anovulation and hyperandrogenism. 5–10% of the female population affected by this syndrome. Nesfatin-1 is a new anorexigenic hormone which is expressed from several regions of hypothalamus and peripheral tissues. Nesfatin-1 is related with obesity, insulin resistance and appetite. We aimed to evaluated the nesfatin-1 levels in patients with PCOS.
Materials and methods
Sixty-five patients (37 patients with PCOS and 28 healthy control subjects) were enrolled in the study. We included newly diagnosed patients with PCOS in our study. Diagnosis of PCOS was based on the 2003 ESHRE/ASRM diagnostic criteria.
Results
The patients with PCOS and controls were similar in terms of mean age BMI, W:H ratio and HOMA–IR index. Plasma nesfatin-1 levels were similar between groups. There was no correlation between plasma nesfatin-1 levels and other parameters.
Conclusion
In conclusion nesfatin-1 may be play important role in glucose metabolism and insulin resistance. In this study due to the absence of insulin resistance in PCOS patients, levels of nesfatin-1 were similar with control group. Nesfatin levels were associated with glucose metabolism, but further studies are needed in this regard.

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P621

Pregnancy in women with polycystic ovary syndrome is associated with higher risk of gestational diabetes mellitus, but not of other adverse obstetric outcomes

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Background
Polycystic ovary syndrome (PCOS) is associated with obesity and increased risk of type 2 diabetes mellitus.
Aim
The aim of the present prospective cohort study was to investigate possible associations between PCOS and obstetric outcomes in 199 Danish women with PCOS and 995 controls and to describe the impact of different PCOS phenotypes on the risk of adverse obstetric outcomes.
Methods
Women diagnosed with PCOS at Odense University Hospital who had singleton pregnancies and childbirths during 2003–2011 ($n=199$) were identified. A control group was matched to the study cohort according to date of childbirth ($n=995$). Data on maternal age, parity, pre-gestational BMI, gestational diabetes mellitus (GDM), pregnancy induced hypertension (PIH), preeclampsia, shoulder dystocia, instrumental delivery and caesarean delivery and data on gestational age and size at birth and Apgar score in the offspring were prospectively collected.
Results
Pre-gestational BMI was significantly higher in women with PCOS than controls, median (quartiles): 26.0 (22.0-31.6) vs 23.2 (20.9-26.1) kg/m^2, $P<0.05$. There was no significant difference in parity or age at birth. The risk of GDM was significantly increased in women with PCOS compared to controls (odds ratio (95% CI) 4.69 (2.30-9.56). The odds ratio was 3.25 (1.54–6.88) after adjustment for age, parity and BMI. The risk of PIH and LGA was increased in women with PCOS vs controls but there was no difference after adjustment for age, parity and BMI. In analysis of LGA, GDM was also included as a possible confounder. Individual PCOS phenotypes were not associated to obstetric outcomes in PCOS.
Conclusions
PCOS is associated with increased risk of GDM. PCOS does not significantly increase the risk of other adverse obstetric outcomes.

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P622

Study on pregnancy outcomes in patients with type 1 diabetes mellitus having self-control skills

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The work was initiated to study peculiarities of pregnancy in patients with prepubertal onset of type 1 diabetes mellitus (T1DM).
We examined 22 patients with prepubertal onset of T1DM. Glycemia and HbA1c levels were measured to assess carbohydrate metabolism. All patients were examined in compliance with protocol of management for patients with pre-gestational diabetes.
Mean age of the examinees, primagravidas, was 21.4±4.7, the disease onset age and duration being 10.8±4.7 and 12.8±4.5 respectively. Pre-gestational, gestational and post-gestational HbA1c was 8.7±1.3, 6.72±1.4 and 8.6±1.4% respectively, that is, as it can be seen, reduced through pregnancy. 22 patients received intensive basal-bolus therapy with recombinant human insulin, daily dose requirement changing by gestational age. Thus, daily doses in the first and second trimesters were 45.6±12.0 and 49.6±14.6 U/d, respectively, the one after delivery being 47.6±9.8 U. Hypoglycemic episodes were registered almost in all examinees two to three times a week in the first half of pregnancy, severe hypoglycemia being observed in three patients, the severest one through coma being registered in one patient. As to vascular complications, diabetic retinopathy of various degrees was found in 13 patients (59%), IV–V degree diabetic nephropathy being found in four, one woman having I degree chronic kidney deficiency. Despite contraindications to pregnancy prolongation in patients with IV–V degree diabetic nephropathy and having I degree chronic kidney deficiency, the pregnancies were not terminated. Diabetic nephropathy was found progressing, but transient and resolving in 6 months after delivery. As to pregnancy outcomes, therapeutic abortion was performed in four patients, due to morning sickness in one woman and to deterioration of the kidneys in three. Cesarean section was performed at various gestational ages in 16 (88.8%), at 34–35 weeks in four patients, at 36–37 weeks in six women, at 38–39 weeks in another six. Natural delivery was performed in two patients at 38–39 weeks.
Prepubertal DM onset poses high risk of complications in pregnancy. Risk of unfavorable pregnancy outcome is the highest one upon prolongation of pregnancy with contraindications.

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P623

Liver enzymes in normal-weight women with polycystic ovary syndrome

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Introduction
Women with PCOS have increased risk for non-alcoholic fatty liver disease (NAFLD). Alanine aminotransferase (ALT) is a sensitive indicator of liver cell injury. The aim of this study is to determine levels of liver enzymes in normal-weight women with PCOS.
Methods
PCOS was diagnosed using ESHRE/ASRM criteria. Normal weight was defined as BMI $\leq$25 kg/m^2. We evaluated 62 normal weight women with PCOS (PCOS group: 20.99±1.92 kg/m^2; 24.76±4.23 years) and 28 normal weight, BMI-matched healthy women (control group: 21.79±2.14 kg/m^2; 30.93±5.63 years). Because groups differed in age ($P<0.001$), statistical analyses were adjusted for age. Blood samples were collected in follicular phase of menstrual cycle for determination of ALT, AST, gamma-GT (GGT), basal glucose, insulin, total-cholesterol (TC), HDL-cholesterol (HDL), LDL-cholesterol (LDL), triglycerides, testosterone and SHBG. HOMA–IR was calculated using standard formula.
Results
PCOS had significantly higher testosterone (2.5±0.9 vs 1.2±0.4 nmol/l; $P<0.001$), ALT (21.8±10.0 vs 16.6±8.2 U/l; $P=0.015$), basal glucose (5.0±0.4 vs 4.6±0.3 mmol/l; $P=0.001$), insulin (15.3±7.9 vs 8.6±3.4 mU/l;

$P<0.001$), HOMA (3.1±1.6 vs 1.9±0.8; $P=0.005$); triglycerides (0.9±0.4 vs 0.8±0.3 mmol/l; $P=0.009$), lower SHBG (42.3±21.9 vs 67.2±33.1 nmol/l; $P=0.001$) and AST/ALT (0.9±0.4 vs 1.3±0.4; $P=0.001$). There was no difference in other parameters between the groups ($P>0.05$). ALT correlated with triglycerides ($r=0.303$, $P=0.017$) and SHBG ($r=-0.260$, $P=0.041$).
Conclusion
Results of our group of PCOS women showing higher ALT level and AST:ALT ratio, may implicate on the presence of NAFLD irrespectively of body weight in those subjects.

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P624

Prevalence of metabolic syndrome in obese women with polycystic ovary syndrome

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Introduction
Women with polycystic ovary syndrome (PCOS) have higher prevalence of metabolic syndrome (MS) than healthy women. However, it is still unclear weather this is a consequence of PCOS *per se* or higher prevalence of obesity in this population. The aim of this study was to determine prevalence of MS in obese women with PCOS.
Methods
PCOS was diagnosed using ESHRE/ASRM criteria. Obesity was defined as BMI ≥25 kg/m^2. We evaluated 100 obese women with PCOS (PCOS group: 30.9±3.3 kg/m^2; 30.1±2.0 years) and 50 obese, age- and BMI-matched healthy women (control group: 30.4±3.0 kg/m^2; 31.0±2.7 years). MS was diagnosed according to NCEP–ATP III criteria. In all subjects blood pressure (BP) and waist circumference (WC) were determined. Blood samples were collected in follicular phase of menstrual cycle for determination of basal glucose, insulin, HDL-cholesterol, triglycerides, uric acid (UA). Homeostatic model assessment (HOMA) was used to determine insulin resistance.
Results
PCOS in comparison to controls had significantly higher WC (93.8±8.0 vs 90.9±9.2 cm; $P=0.040$), insulin (15.4±8.2 vs 10.7±5.5 mU/l; $P<0.001$), HOMA (3.7±2.2 vs 2.6±1.3; $P=0.001$); triglycerides (1.4±0.6 vs 1.0±0.4 mmol/l; $P<0.001$), UA (299.9±70.7 vs 269.7±48.1 μmol/l; $P=0.008$) and lower HDL (1.1±0.2 vs 1.2±0.2 mmol/l; $P=0.031$). There was no difference in BP ($P=0.983$) and basal glucose ($P=0.063$) between the groups. MS prevalence was significantly higher in PCOS group in comparison to controls (PCOS: 43/100 (43%); controls 6/50 (12%); $P<0.001$). Of those PCOS who had MS, three criteria were fulfilled in 32%, four in 10% and all five criteria were fulfilled 1% of PCOS.
Conclusion
In comparison to age and BMI matched healthy women, prevalence of metabolic syndrome defined by NCEP–ATP III criteria was higher in our group of obese women with PCOS.

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P625

Prevalence of dysglycaemia in obese women with polycystic ovary syndrome

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Introduction
Insulin resistance and obesity are common features of polycystic ovary syndrome (PCOS) and both are independently associated with dysglycaemia. The aim of this study was to determine prevalence of dysglycaemia in obese women with PCOS.
Methods
PCOS was diagnosed using ESHRE/ASRM criteria. Obesity was defined as BMI ≥25 kg/m^2. We evaluated 100 obese women with PCOS (PCOS group: 28.99±3.05 kg/m^2; 27.70±5.89 years) and 50 obese, age- and BMI-matched healthy women (control group: 28.13±3.77 kg/m^2; 28.58±3.43 years). There was no difference in age and BMI between the groups ($P=0.101$ and $P=0.137$ respectively). Blood samples were collected in follicular phase of menstrual cycle for determination of basal glucose, insulin, total-cholesterol (TC), HDL-cholesterol (HDL) and LDL-cholesterol (LDL), and triglycerides. Two-hour oral glucose tolerance test (OGTT) with 75 g of glucose was performed in all subjects. Homeostatic model assessment (HOMA) was used to determine insulin resistance. Impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and diabetes mellitus (DM) were defined according to American Diabetes Association (ADA) criteria.
Results
PCOS had significantly higher basal glucose (5.8±0.7 vs 5.3±0.5 mmol/l; $P=0.001$), insulin (14.3±10.3 vs 9.6±5.2 mU/l; $P=0.002$), HOMA (3.6±2.5 vs 2.3±1.3; $P<0.001$); and triglycerides (1.1±0.4 vs 0.9±0.4 mmol/l; $P=0.009$). There was no difference in TC, HDL and LDL between the groups ($P>0.05$). PCOS had higher prevalence of IFG (50/100 (50%) vs 3/50 (6%); $P<0.001$) and IGT (43/100 (43%) vs 3/50 (6%); $P<0.001$), while there was no difference in prevalence of DM (5/100 (5%) vs 1/50 (2%); $P=0.664$).
Conclusion
In comparison to age and BMI matched healthy women, prevalence of impaired fasting glucose and impaired glucose tolerance was higher in our group of obese women with PCOS, while there was no difference in prevalence of diabetes mellitus.

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P626

Simultaneous determination of salivary androgens by liquid chromatography–tandem mass spectrometry: analytical and biological validation

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The hormone assessment in saliva is emerging as a new valuable tool for clinical and research purposes. Salivary levels are supposed to reflect the free fraction of circulating steroids, thus representing a more informative indicator of their activity. Moreover, saliva collection is not stressful and does not require medical assistance, allowing reliable and multiple sampling in a day. Liquid chromatography–tandem mass spectrometry (LC–MS/MS) technology offers high sensitivity and specificity to detect small concentration, and allows multi-analyte quantitation. In this study, we developed and validated a LC–MS/MS method for the simultaneous measurement of salivary testosterone, androstenedione, DHEA and 17OHProgesterone (17OHP), achieving a functional sensitivity (imprecision, accuracy) of 0.95 pg/ml (2.3–108%), 1.95 pg/ml (14.1–104%), 78.1 pg/ml (8.1–102%) and 15.6 pg/ml (13.2–89%) for testosterone, androstenedione, DHEA and 17OHP, respectively. For biological validation, paired serum and saliva samples were collected from 12 males and seven females healthy, normal weight adult volunteers, at 800, 1200, 1600, and 2000 h of a regular day. We measured saliva androgen by the novel assay and serum androgens with a dedicated LC–MS/MS method previously validated. Free testosterone was calculated by the Vermeulen formula, by measuring SHBG and albumin concentrations at each time point. Salivary androgens were highly correlated to serum androgens (A: $r=0.919$; DHEA: $r=0.771$; 17OHP: $r=0.875$; female T: $r=0.842$ and male T: $r=0.874$). Moreover, a high correlation was observed also between salivary testosterone and free testosterone both in females ($r=0.886$) and males ($r=0.860$). Our assay displayed the sensitivity, accuracy and precision needed for a proper measurement of low salivary androgens concentrations and for its application in epidemiological studies or in routine settings. Moreover, the multi-analytical profiling allows a more effective evaluation of androgen status and will be used to define the reference ranges and circadian rhythm in healthy as well as in hypogonadic or hyperandrogenic subjects.

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P627

Mosaic Turner syndrome and pituitary microadenoma in patient with polyglandular autoimmune syndrome type II

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Introduction
Polyglandular autoimmune syndrome type II (PGA-II) is the most common immunoendocrinopathy syndrome, characterized by the obligatory occurrence of Addison disease in combination with thyroid autoimmune diseases and/or type 1 diabetes mellitus. This case report presents coexistence of mosaic Turner syndrome and pituitary micoradenoma in patient with PGA-II.
Case report
A 30-year-old women underwent IVF for four times, with no success (always poor ovarian response, double embryo transfer). Hashimoto's thyroiditis and subclinical hypothyreoidismus were treated with levothyroxine substitution. Patient's karyotype testing shown a mosaic monosomy X (46, XX/45, X0), with 5% of analyzed cells caracterized by monosomy X, but no syndrome phenotype characteristics, entered puberty at the time, regular menstrual cycles and no echocardiography dysgenetic ovarian characteristics. NMR sellar region shown microadenoma in the right half. Repeatedly elevated prolactin level in the morning, but preserved circadian rhythm and daily values in the referent range. No adequate cortisol answer in insulin tolerance test, but normal prolactine and GH. In TRH test no paradoxal response. During the last IVF no follicle on folitropine stimulation was found, and for the first time higher FSH value and lower AMH value were found, indicating premature ovarian insuffuciency; antiovarian antibodies were negative excluding immune-mediated process. A year later, menstrual cycles became irregular. Two years later she presented with sings of hypocorticisam (artralgia, hyperpigmentation, fatigue and hypotension) and low corisol level, but normal electrolyte level, hydrocortisone substitution was started. PTH was in referent range. Positive anti GAD and anti IA2 antibodies were demonstrated, oral glucose tolerance test was normal. Patient is now in oocyte donation process.
Conclusions
Oocyte donation may offer solution to women with multiple autoimmune disorder causing infertility.

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P628

New endocrine and intracellular regulators of reproductive functions

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Progress in reproductive medicine, assisted reproduction, veterinary medicine and animal production and biotechnology is promoted by discovery and application of the new extra- and intracellular regulators of reproductive functions. This is the review of original data concerning the role of some metabolic hormones (GH, leptin, ghrelin and obestatin), growth factors (IGF1, IGFBPs, EGF and thrombopoietin), intracellular mediators of their action (cyclic nucleotides, protein kinases, transcription factors and related cDNA, siRNA and miRNA gene constructs) on basic ovarian functions (cell proliferation, apoptosis, secretion, oogenesis, ovulation, production and viability of pups) in different species (pig, rabbit, humans and chicken). Practical applications of some these molecules for characterisation, prediction and control of reproductive processes in these species was examined too. It was shown that these hormonal and intracellular regulators are able to control apoptosis, proliferation and secretory activity in porcine, rabbit, human and chicken ovarian cells and maturation of porcine oocytes and cumulus oophorus *in vivo* and *in vitro*, as well as to suppress or promote the response of ovarian cells to other hormones (gonadotrophins, IGF1 and ghrelin). Our results suggest, that metabolic hormones, growth factors and intracellular regulators and mediators of their action (protein kinases, transcription factors, siRNAs and miRNAs) can be used for characterization of state of ovarian cells, for identification signaling pathways (hormones-growth factors-protein kinases-transcription factors-genes regulating proliferation, apoptosis and secretory activity) controlling reproductive processes, as well as for prediction and control of basic ovarian cell functions (proliferation, apoptosis, secretory activity, maturation of oocyte–cumulus complex and fertility).

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P629

Birth weight is associated with important clinical and biochemical parameters of PCOS

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Introduction
Several studies have demonstrated associations of birth weight with metabolic and reproductive abnormalities in adults. The aim of this study was to investigate the birth weight in women with PCOS and its correlation with important clinical and biochemical parameters of the syndrome.
Patients and methods
We studied 288 women with PCOS according to the NIH criteria (1990) and 166 women with normal cycles and without clinical or biochemical hyperandrogenemia. Birth weight and anthropometric characteristics were recorded. After an overnight fast, androgens, sex hormone binding globulin (SHBG), insulin and fasting glucose were measured.
Results
Information on birth weight was available for 224/288 women with PCOS and 75/166 controls. No differences were found ($P>0.05$) in birth weight, between women with PCOS (3228 ± 530 g) and normal controls (3160 ± 503 g). In women with PCOS, birth weight was negatively correlated with DHEAS levels ($P=0.04$, $r=-0.137$) and positively correlated with the waist circumference ($P<0.001$, $r=0.312$) and BMI ($P=0.04$, $r=0.136$). In controls, birth weight was only negatively correlated with SHBG levels ($P=0.026$, $r=-0.263$). Then, we divided women from both groups in six categories according to birth weight (A. <2500 g, B. 2501–3000 g, C. 3001–3500 g, D. 3501–4000 g, E. 4001–4500 g, F. >4.500 g). We observed no statistically significant differences in the distribution percentages among those with PCOS and normal controls (A. 8 vs 12%, B. 26.8 vs 22.7%, C. 38.4 vs 40%, D. 21.4 vs 25.3%, E. 4.5 vs 0%, F. 0.9 vs 0%) (for all $P>0.05$). We found a trend for difference regarding category E ($P=0.059$).
Conclusions
Women with PCOS do not differ in birth weight from women with normal cycles. However, birth weight is associated with important clinical and biochemical parameters of the syndrome including obesity and hyperandrogenism.

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P630

Expression of P450arom mRNA in the ovary and brain of Indian teleosts, *Labeo rohita* and *Anabas testudineus*: seasonal variation and effects of gonadotropin

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The *cyp19* encodes cytochrome P450aromatase, the key enzyme catalyzing the conversion of androgens to estrogens. Estrogens play a critical role in controlling functional, behavioral and physiological aspects of sexual development both in males and females. Except in *Anguilla anguilla*, most teleosts studied so far possess two *cyp19* genes namely, *cyp19a* and *cyp19b*; ovary- and brain-specific respectively. In the present study made in two fishes, *Labeo rohita,* a major carp and *Anabas testudineus,* a climbing perch, we found a very high expression of ovary-specific *cyp19a* mRNA in the ovary of both the fishes. Partial sequencing of cDNA product of *cyp19a* genes of both the teleosts revealed a high degree of homology with *cyp19a* cDNA sequences of other teleosts. Comparative seasonal analyses of the expression of *cyp19a* mRNA and its protein in these two teleosts showed increased expression of this gene in the ovary of vitellogenic and post vitellogenic stages fish. HCG induced a profound stimulatory effect on the expression of ovarian *cyp19a* mRNA and its protein in both the fishes. Interestingly, *cyp19b*-specific primers used in semi-quantitative RT-PCR analyses gave ~300 bp fragment in the brain of both the fishes. Results showed that *cyp19a* mRNA expression in the ovary was dependent on the seasonal reproductive variation, however it was not so in the brain. Overlapping expression of *cyp19a* and *cyp19b* mRNAs were also detected in ovary and brain of both the teleosts. The physiological and functional significance of the presence of *cyp19a* and *cyp19b* in the ovary and brain of these two fishes has been discussed.

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P631

The relationship between clinico-biochemical features in women with polycystic ovary syndrome and fertility treatment outcomes

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Introduction
Polycystic ovary syndrome (PCOS) affects 5–8% of reproductive-age women. The morbidity related to PCOS may include insulin-resistance, type 2 diabetes mellitus (T2DM), obesity, hypertension, cardiovascular disease and infertility. We aimed to evaluate the clinico-biochemical characteristics of PCOS women and establish its relationship with fertility treatment outcomes.
Methods
We reviewed clinical records of PCOS women (Rotterdam criteria, 2003) surveilled at Hospital Santa Maria, between 2004 and June 2013. Fertility treatment outcomes were defined as: i) obtention of pregnancy; ii) number of treatment cycles; and iii) effective duration of the treatments.
Results
We identified 229 PCOS women. The mean age was 29.7 ($\pm$3.8) years. The infertility time was estimated in 41 ($\pm$29) months and 80.8% were primary infertilities. Out of the 229 women, 134 (58.5%) were obese, 169 (73.8%) had waist circumference $>$80 cm, 12 (5.2%) were hypertensive, 61 (26.6%) were smokers and 72 (31.4%) had familial history of T2DM. Clinical and/or biochemical androgen excess was detected in 110 (48%). Glucose abnormalities, insulin-resistance, hypertriglyceridemia, low cholesterol-HDL were detected in 23 (10%), 78 (34.1%), 15 (6.6%) and 93 (40.6%), respectively.
Pregnancy was achieved in 164 (71.6%) women. Spontaneous abortion was verified in 29 (12.7%) women (five had more than one). The mean number of treatment cycles needed was 2.8 ($\pm$2.4) and the mean duration of effective treatment estimated in 7.5 ($\pm$1) months. Pharmacological induced-ovulation was the most common approach.
Bi-model univariate and multivariate analysis, regarding to the identification of factors associated with longer fertility treatments/higher number of treatments, detected with statistical significance: secondary infertility; T2DM familial history, hypertriglyceridemia and low cholesterol-HDL. Other factors as age, obesity, waist circumference $>$80 cm, hypertension, smoking habits, clinical or biochemical androgen excess, glucose abnormalities, insulin-resistance or hypertension were not associated with poorer fertility treatment outcomes.
Conclusion
Infertile PCOS women with secondary type infertility, T2DM familial history, hypertriglyceridemia and low cholesterol-HDL may have poorer fertility treatment results, possibly justifying more intensive approaches. Other clinico-biochemical characteristics seem not to have prognostic value for fertility treatment.

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P632

Primary amenorrhea due to gonadal disgenesis: chromosome 13 abnormality not detected previously: a case report

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Background
X and Y chromosomes carry many genes that direct development and gametogenesis. Rearrangements associated with X chromosome may have a role in abnormal phenotypes. We presented a case of primary amenorrhea with normal karyotype but centromere thickness in 13th chromosome (13 cenh$^+$), this is the first case in literature.
Case
A 18-year-old woman admitted to endocrinology clinic with complaints of primary amenorrhea and a failure in breast development. Her medical history was insignificant. In physical examination her height, weight and BMI were 1.61 m, 48.5 kg and 20 kg/m^2 respectively. Axillary and pubic hair were Tanner stages 2–3, breast was stage 2. The patient had not facial dysmorphism, webbed neck and skeletal abnormalities. Complete blood count and biochemical values were normal. Hormonal evaluation revealed hypergonadotropic hypogonadism (LH: 28.8 mU/ml, FSH: 57 mU/ml, estradiol: 10 pg/ml) and normal prolactin and thyroid function tests. Karyotype analysis was performed with GTG (Giemsa-Trypsin) banding technique and 46, XX, 13 cent$^+$ chromosome abnormality was detected. Band thickness in centromere region and increase in centromere heterochromatine length of chromosome 13 were detected. Pelvic MR revealed no ovaries and normal uterus. Hypophysis MR was normal. For breast development estrogen treatment was started and then changed to combined estrogen and progesterone treatment. After treatment patient's menstrual cycles were started and patient is under follow up for 3 years.
Discussion
Premature ovarian failure (POF) may present with primary or secondary amenorrhea. POF has many causes include increased atresia due to chromosomal abnormalities, autoimmune diseases, infections, radiation and chemotherapy. A terminal rearrangement in chromosomes 13 and 20 was presented in a patient with primary amenorrhea. In our case 46, XX, 13cenh$^+$ was detected. This abnormality was not presented in literature previously. But we know various dislocations and deletions in X chromosome may cause gonadal disgenesis in light of previous literature. Therefore we speculate that an association may be present between centromere thickness in 13th chromosome and gonadal disgenesis in our case.

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P633

Increased occurrence of proinflammatory IL17, IL6 and MCP-1 cytokines and resistin with the overweight-associated polycystic ovarian syndrome, pituitary adenome and obesity

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Adipose tissue acts as a metabolically dynamic endocrine organ secreting several hormones, cytokines, chemokines and growth factors. Resistin plays a role in inducing insulin resistance and inflammation mediated by IL6 and MCP1 cytokines. Polycystic ovarian syndrome (PCOS), pituitary adenoma (PA) and obesity disorders are characterized by insulin resistance and different hormonal-metabolic processes.
The increased occurrence of proinflammatory IL17, IL6 and monocyte chemo-attractant protein-1 (MCP1) cytokines and resistin was investigated, which are initiating factors for cardiovascular diseases and atherosclerosis.
Ninety fertile women (mean age 35 years and mean body mass index (BMI) 28), of whom 16 women were controls, 28 women had polycystic ovarian syndrome, 9 women had pituitary microadenome and 37 women obesity. The serum cytokine measurements were performed by ELISA.
All cytokine levels were higher in obesity compared with those in controls (65.86 ± 41.76 vs 48 ± 20.45 ng/ml, $P<0.042$ for resistin; 12.38 ± 3.01 vs 10.44 ± 0.54 ng/ml, $P<0.0001$ for IL17; 22.57 ± 6.9 vs 16.32 ± 2.29 ng/ml, $P<0.0001$ for IL6; 19.54 ± 3.03 vs 15.93 ± 0.56 ng/ml, $P<0.0001$ for MCP1). Increased IL17 (14.13 ± 3.79 ng/ml, $P>0.0001$) and MCP1 (17.8 ± 2.71 ng/ml, $P<0.001$) levels were demonstrated in PCOS and lower resistin levels (44.8 ± 22.08 ng/ml, $P<0.03$) in PA patients in comparison with those in controls. A strong relationship was found between resistin and IL6 ($P<0.002$, $r=0.3256$), between IL6 and IL17 ($P<0.0001$, $r=0.4074$) or MCP1 ((P 0.0001, $r=0.6237$), as well as between IL17 and MCP1 (P 0.0001, $r=0.6253$).
Overweight in PCOS and obesity represents an accelerating factor for cardiovascular diseases and atherosclerosis through increased proinflammatory cytokine secretion. IL17 cytokine levels enhance also in overweight and it be involved in inflammatory processes.

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P634

Mice lacking anti-Müllerian hormone signaling are protected against the age-related decline in metabolism

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Polycystic ovary syndrome (PCOS) is a disorder associated with infertility and metabolic disturbances. Ovaries of PCOS women contain an increased number of growing follicles. Such an ovarian phenotype is also observed in mice lacking the ovary-specific growth factor anti-Müllerian hormone (AMH). To determine the interaction between ovarian and metabolic function, we studied the metabolic phenotype of mice lacking AMH signaling as a model for an altered profile in ovarian growth factors.
Female mice lacking AMH (AMHKO) or its specific type 2 receptor (MRKI) and WT littermates (WT) were analyzed at 4, 5 and 8 months of age. Body weight, white and brown adipose tissue (WAT and BAT) weight, and serum adipokine levels were measured, and an intraperitoneal glucose tolerance test (IPGTT) was performed.
Body weight did not differ between genotypes. Similarly, glucose tolerance did not differ at 4 months. However, at 5 months of age, AMHKO and MRKI mice had a better glucose tolerance than WT mice ($P=0.002$), who displayed a worsening in glucose tolerance with increasing age. At 5 months, WAT depots of AMHKO and MRKI mice weighed 10–40% less and contained smaller adipocytes ($P<0.001$). In agreement, leptin levels were 40–80% reduced in AMHKO and MRKI mice compared to WT mice. Interestingly, AMHKO and MRKI mice had more active BAT and displayed increased browning of WAT, illustrated by increased UCP1 staining in WAT compared to WT mice. At 8 months, AMHKO mice continued to have smaller adipocytes ($P<0.001$), lower leptin levels ($P<0.05$), and tended to have improved glucose tolerance ($P<0.07$) combined with lower insulin levels ($P<0.05$) compared to WT mice.
In conclusion, in the absence of AMH signaling mice are protected against the age-related worsening in metabolism. This suggests that an altered profile in ovarian growth factors may affect metabolism and may modulate the effect of metabolic aging.

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P635

Thyroid disorders in young females with polycystic ovary syndrome: is thyroid volume associated with serum IGF1 level?

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Background
PCOS is one of the most common disorders affecting at least 5–10% of women of reproductive age. Increased prevalance of autoimmune thyroiditis and goiter were reported in PCOS patients. This study investigated the prevalance of hypothyroidism, thyroid autoimmunity, ultrasonographic features and presence of nodules in PCOS patients and compare them with the control group. We also aimed to detect correlation of thyroid volume (TV) with serum IGF1 levels in patients with PCOS.
Method
Seventy PCOS patients and 84 age matched controls were enrolled. Patient group and the control group were compared with each other according to hormonal parameters, anthropometric measures, thyroid volume, echogenicity on USG and autoimmunity. We also investigated the correlation between TV and IGF1 level in the PCOS group.
Results
BMI, Ferriman–Gallwey score (FGS), fasting insulin level, DHEA-S, total and free testosterone, LH, thyroid volume and IGF binding protein-3 (IGFBP-3) levels were significantly higher in PCOS patients compared to the control group. Thyroid volume was similar in patients with or without insulin resistance diagnosed with HOMA-IR. There was no difference according to prevalence of hypothyroidism or ultrasonographic features, in between the groups. We have detected a positive and significant correlation between TV and BMI. We have found that there was no meaningful correlation between the TV and serum IGF1 levels.
Conclusion
This is the first study about thyroid volume and IGF1 correlation in those group of patients. There is need for further studies with lager number of patients.

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P636

The prevalence of autoimmune thyroiditis and hypothyroidism in PCOS women

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Context
Both polycystic ovary syndrome (PCOS) and chronic autoimmune thyroiditis (AIT, Hashimoto disease) are common endocrinopathies and the AIT is the most prevalent cause of hypothyroidism in areas with sufficient iodine intake. Patients with PCOS are probably more susceptible to the development of autoimmune diseases. The data about the prevalence of AIT in PCOS is limited and it has not been assessed in the Polish population.
The aims of the study were: to assess the prevalence of AIT and hypothyroidism in PCOS patients.
Subjects and methods
We analyzed data of 199 young (mean 25 years of age) PCOS women, who were the patients of our Endocrinology Department (years 2009–2012), in whom PCOS was recognized with AES Criteria and TSH, fT_4, thyroid antibodies and thyroid USG were performed.
Results
i) In the PCOS group: AIT was present in 67 women (33.7%), markedly increased thyroid antibodies (anty-TPOab or anty-TGab) were present in 62 patients (31.2%) and the ultrasound changes typical of AIT were found in 87 women (43.7%). ii) TSH level in the whole group was 1.8 mU/l (mean value), while in AIT group vs non-AIT group was 2.41 vs 1.47 mU/l; $P<0.05$. iii) TSH higher than 2.5 mU/l or within normal range, but in patients taking L-thyroxin, was present in 39 women (19.5%) of the whole group and in 27 (40.3%) women with AIT.
Conclusions
i) AIT is a very common disease in patients with PCOS. ii) PCOS women with AIT have statistically significant higher TSH levels than PCOS women without AIT. iii) Subclinical or evident hypothyroidism is present in about 20% of PCOS women and in about 40% PCOS women with AIT. iv) All PCOS patients should be screened for Hashimoto disease and hypothyroidism.

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P637

Systolic blood pressure and fatty acid-binding protein 4 predict pregnancy-induced hypertension in overweight nulliparous women

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Objectives
The insulin-sensitivity regulator adipocyte fatty acid-binding protein 4 (FABP4) integrates metabolic and inflammatory responses. We hypothesize that there is relationship between FABP4 and factors related to metabolic syndrome in pregnancy-induced hypertension (PIH).
Materials and methods
In this prospective observational study, among the 72 relatively overweight ($BMI \geq 24\ kg/m^2$) nulliparous women, 14 developed non-proteinuric PIH and 12 developed proteinuric PIH (preeclampsia), whereas 46 had normotensive pregnancies. was assessed insulin sensitivity via the whole-body insulin sensitivity index (ISI) and the homeostatic model of assessment – insulin resistance (HOMA-IR) at 24 weeks of gestation. Maternal serum levels of FABP4, high-sensitive C-reactive protein (hs-CRP), total testosterone, SHBG and non-protein-bound calculated free testosterone (cfT) were determined at 24 and 32 weeks.
Results
Measures of ISI, HOMA-IR, hs-CRP, testosterone and lipids did not differ at 24 and/or at 32 weeks in women who were subsequently hypertensive. SBP was higher at all time points and FABP4 levels tended to be higher at 24 and 32 weeks in patients compared to controls. In logistic regression analysis, baseline FABP4 ($P=0.04$, $r^2=0.06$) and SBP after 10 min standing ($P=0.015$, $r^2=0.09$) were associated with the development of PIH. FABP4 levels at 24 weeks did not correlate with insulin sensitivity. Neither was correlation seen between FABP4 levels at 24 and 32 weeks, vs those of hs-CRP and testosterone.

Conclusions
This prospective study showed that the serum FABP4 concentration and SBP after 10 min standing at 24 weeks are associated with the development of PIH.

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P638

Wolfram syndrome with hypergonadotropic hypogonadism: case report

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Introduction
Wolfram syndrome has characterized by central diabetes insipidus (DI), diabetes mellitus (DM), optic atrophy (OA) and deafness. In this report we presented a Wolfram syndrome with hypergonadotropic hypogonadism.
Case
A 18-year-old girl who has diabetes for 6 years was hospitalized due to blood sugar irregularity. Her medical history revealed frequent urination and enuresis for 2–3 years and primary amenorrhea. Furthermore she had hear and visual decrease for 2–3 months. She did not finish primary school due to frequent hypoglycemia and learning disability. In physical examination blood pressure, pulse, height and weight were 110/70 mmHg, 72 beats/min, 143 cm and 43 kg respectively, breast development was Tanner stage 1, axillary and pubic hair were Tanner stages 1–2. In laboratory fasting blood glucose, HbA1c, creatinine, FSH, LH, estradiol and urine density were 275 mg/dl, 13.6%, 0.7 mg/dl, 49.91 mU/ml, 28.065 mU/ml, 25.24 pg/ml and 1004 respectively. In Abdomen ultrasound ovaries were not detected, uterus was hypoplasic. Intravenous pyelography revealed grade 3 hydroureteronephrosis in both kidney. After urodynamic and voiding tests neurogenic flask bladder diagnosis was established and intermittent catheterization was suggested to patient. Fluid restriction test was performed for low urine density and result was appropriate for central diabetes insipidus. Visual and auditory evaluation detected optic atrophy and mild bilateral sensorimotor hearing loss. The patient was diagnosed as Wolfram syndrome with DI, DM, optic atrophy, hypergonadotropic hypogonadism and urogenital abnormalities. After a family history evaluation one cousin was evaluated due to diabetes and hear loss and diagnosed as Wolfram syndrome as well.
Discussion
In Wolfram syndrome DM and optic atrophy develop in first decade, DI and sensorineural hear loss develop in second decade, urinary abnormalities develop in third decade and multiple neurologic abnormalities develop in fourth decade. Hypogonadism that seen in Wolfram syndrome is usually hypogonadotropic but rarely hypergonadotropic hypogonadism may be seen. Our patient had hypergonadotropic hypogonadism. All components of Wolfram syndrome was developed in our patient. It is important for early diagnosis and treatment to evaluate type 1 diabetes patients in terms of Wolfram syndrome components, this may prevent complications.

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rhAMH inhibits CYP19 and P450scc mRNA expression in granulosa-lutein cells treated with gonadotropin

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Anti-Mullerian hormone (AMH), a member of transforming growth factor β (TGF-β), shows different sex-related functions. In male, from the fetal development till the puberty, the expression of AMH by Sertoli cells causes regression of Mullerian ducts with subsequent testicular differentiation. Mainly studied in female, AMH produced by ovarian granulosa cells inhibits both initiation of primordial follicle growth and the FSH-stimulated follicle growth. Moreover, recent studies have shown a negative relationship between the *CYP19* mRNA expression, the key enzyme converting androgen to estrogen, and the concentration of AMH retrieved in fluid from small human antral follicles. To our knowledge no data have been produced to clarify the role of AMH on the regulation of expression of the steroidogenic aromatase cholesterol side-chain cleavage (P450scc) which catalyzes conversion of cholesterol to pregnenolone.
In this study, we analyzed the effect of increasing concentrations of rhAMH (range 1–100 ng/ml) at different time point either on CYP19 or P450ssc aromatases expression in primary culture of human granulosa-lutein cells (hGC) recovered from patients who underwent the IVF protocol.
Furthermore, rhAMH (10 ng/ml) was added to colture medium of hGC previously treated for 24 h with rLH (50 ng/ml), rFSH (50 ng/ml) alone or combined. The *CYP19* and *P450scc* mRNA expression, normalized by housekeeping gene *RpS7*, was evaluated by RT-qPCR. Negative controls using corresponding amount of vehicle control for each hormone treatment were performed. Our results show that the strong induction of *CYP19* and *P450scc* mRNA generated by gonadotropins treatment (alone and combined) was reverted by rhAMH although rhAMH alone did not affect aromatases basal expression in any of the concentrations tested.
Results offer new insights to clarify the relationship between hormones leading the early phases of folliculogenesis suggesting that AMH could play a pivotal inhibitory role on both *CYP19* and *P450scc* gene expression in hGC gonadotropin stimulated.

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The obesity effects on features of polycystic ovary syndrome

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Background
Obesity exacerbates many aspects of the PCOS phenotype, especially cardiovascular risk factors, infertility. The objective of the study was to determine the effects of overweight and obesity on the metabolic features of PCOS.
Material and methods
116 PCOS women (according to Rotterdam criteria, mean age 27.16 ± 3.87 years) were investigated in Vilnius city (Lithuania) in 2009–2011. Height, body mass and waist circumference were measured. Participants were tested for FSH, LH, total testosterone, sex hormone-binding globulin (SHBG), DHEAS, estradiol, fasting glucose, fasting insulin, and lipid profile. Free androgen index (FAI) and insulin resistance HOMA-IR index were calculated. PCOS women were divided into three groups according to BMI: 50 normal weight women, 27 overweight women and 39 obese women.
Results
Obese women with PCOS had lower LH compared to normal weight women. Obese and overweight women had more prominent androgen excess compared to normal weight PCOS women (obese FAI = 8.37 ± 4.77, overweight FAI = 6.74 ± 3.13, normal weight FAI = 4.06 ± 2.84, $P < 0.0001$ obese vs normal weight, $P = 0.003$ overweight vs normal weight). 71.8% of obese, 37% of overweight and 16% of normal weight women with PCOS were insulin-resistant. Obese women demonstrated higher by 3.62 HOMA-IR compared to normal weight ($P < 0.0001$) and higher by 3.00 compared to overweight PCOS women ($P < 0.0001$). Obese women with PCOS had lower HDL cholesterol, higher LDL cholesterol and higher triglyceride compared to normal weight PCOS women, and lower HDL cholesterol compared to overweight PCOS women. Overweight PCOS women had lower HDL cholesterol and higher triglyceride compared to normal weight PCOS women. 85.7% of obese, 14.3% of overweight and none of normal weight PCOS women had metabolic syndrome.
Conclusions
Obesity in women with PCOS is significantly associated with worse metabolic features: greater androgen excess, hirsutism, insulin-resistance and dyslipidaemia.

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P641

Relationship between visceral adiposity index, menstrual disorders and hormonal, biochemical and ultrasound parameters in women with polycystic ovary syndrome

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Objective
The clinical phenotype of PCOS includes reproductive and hormonal aberrations. Visceral adiposity index (VAI) is an indicator which could connect hyperandrogenism and anovulation. The objective was to evaluate the relationship between VAI, menstrual disorders and hormonal, biochemical and ultrasound parameters in women with PCOS.
Patients
180 women with PCOS diagnosed with Rotterdam criteria.
Measurements
We correlated VAI with metabolic and clinical features of the syndrome and with indices of inflammation and insulin sensitivity. In addition, we classified the patients into four groups according to the severity of menstrual disorders: Group A ($n=41$), with severe menstrual disorders, Group B ($n=79$), with mild menstrual disorders, Group C ($n=50$), without menstrual disorders and Group D ($n=10$) with women with sychnominorroia.
Results
In women with PCOS studied, VAI significantly correlated with body weight ($r=0.46$, $P<0.001$), fasting glucose ($r=0.31$, $P<0.005$), insulin ($r=0.56$, $P<0.001$), HOMA score ($r=0.51$, $P<0.001$), Matsuda Index ($r=-0.29$, $P<0.001$), white blood cells ($r=0.38$, $P<0.001$), platelets ($r=0.20$, $P<0.05$), uric acid ($r=0.32$, $P<0.001$), free testosterone ($r=0.29$, $P<0.005$), estradiol ($r=0.29$, $P<0.001$), SHBG ($r=-0.22$, $P<0.05$), LDL ($r=0.22$, $P<0.001$), CHOL ($r=0.29$, $P<0.001$), γ-GT ($r=0.32$, $P<0.001$), SGPT ($r=0.22$, $P<0.005$), ultrasound of the liver ($r=0.28$, $P<0.001$) and menstrual cycles per year ($r=-0.25$, $P<0.05$). From the comparison of the four groups, PCOS women with menstrual disorders had significantly higher VAI and HOMA indices when compared to PCOS without menstrual disorders.
Conclusions
VAI is increased in patients with PCOS in concordance with the severity of anovulation, insulin resistance and inflammation. This index could be a very easy and helpful clinical tool in daily practice to predict insulin resistance in women with PCOS.

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P642

Elevated environmental testosterone equivalent concentration in women with polycystic ovary syndrome

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Background
Polycystic ovary syndrome (PCOS) constitutes the most common endocrine disorder in women of reproductive age. Recently, the potential influence of endocrine disrupting chemicals (EDCs) on the development of PCOS has been suggested. The aim of the present study is to determine whether dihydrotestosterone equivalent concentration (DEQ) representing total androgenic activities including androgen derivatives from EDCs measured by chemically activated luciferase gene expression (CALUX) bioassay is different in women with PCOS compared to controls and associated with hormonal and metabolic features of PCOS.
Methods
We recruited 99 women with PCOS (26 ± 4 years) and 100 healthy women with regular menstrual cycles (26 ± 4 years), and performed a case–control association study. Anthropometric, hormonal, and biochemical measurements and ovarian ultrasound were performed. DEQ levels were determined using CALUX bioassay.
Results
DEQ levels were significantly higher in women with PCOS compared to controls (425.1 ± 360.3 vs 89.6 ± 53.5 pg/l, $P<0.05$), regardless of obesity. DEQ levels in women with PCOS did not differ according to hyperandrogenism, obesity, and polycystic ovaries. DEQ levels were not correlated with clinical, hormonal, and metabolic variables in women with PCOS.
Conclusion
DEQ levels were higher in women with PCOS compared to controls. But DEQ levels did not have any association with hormonal and metabolic features of PCOS. DEQ may have a role in the development of PCOS, but further prospective study using DEQ will be required to determine the exact action on the development of PCOS.

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P643

The *FSHR* polymorphism p.N680S mediates different response kinetics to FSH *in vitro*

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Introduction
FSH acts on its receptor (FSHR) resulting in signal transduction activation, gene expression and steroidogenesis. The *FSHR* common SNP p.N680S is a marker of gonadal response *in vivo*. However, *in vitro* dose–response experiments failed to demonstrate the molecular basis thereof so far. In this study, we systematically investigated whether p.N680S mediates different kinetics of FSH response *in vitro*.
Design
We evaluated the activation kinetics of cAMP, phERK1/2, phCREB by ELISA and western blotting in *FSHR* homozygous, primary, human granulosa lutein cells (hGLC-680N, -680S) stimulated by 50 nM r-FSH for up to 2 h (short-term stimulation). Following short-term stimulation the expression of target genes was evaluated by real-time PCR after 12 h, and progesterone production kinetics over 24 h. Specific inhibitors/agonists (U0126, PMA) were used in the presence and in the absence of FSH.
Results
Intracellular cAMP increased within 5–10 min in hGLC-680N, reaching the *plateau* in about 45 min. cAMP increase was delayed in hGLC-680S, reaching the *plateau* in 120 min, revealing different activation kinetics (Mann–Whitney *U* test; $P<0.05$; $n=4$). r-FSH-dependent cAMP stimulation kinetics resulted in different ERK1/2 and CREB phosphorylation, reaching maximal levels in 5–30 min in hGLC-680N, whereas, in hGLC-680S, these were weaker and steady over 2 h (Mann–Whitney *U* test; $P<0.05$; $n=3$). hGLC-680N stimulation resulted in higher expression levels of *AREG* and *StAR* (Mann–Whitney *U* test; $P<0.05$; $n=4$) and in subsequently different progesterone production kinetics, achieving overall higher levels in hGLC-680N vs -680S (Mann–Whitney *U* test; $P<0.05$; $n=3$). Interestingly, the different kinetics of progesterone production between hGLC-680N and -680S were interchanged by selective phospho-ERK1/2 blockade/activation through specific inhibitor/agonist, revealing a short-term cross-talk mediated by ERK1/2.
Conclusions
This study demonstrates for the first time *in vitro,* how FSHR p.N680S mediates different response to FSH, resulting in different kinetics of cAMP, phERK1/2 and phCREB activation, and progesterone production.

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P644

The PCOS evolutionary paradox: a GWAS-based, *in silico*, evolutionary explanation

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Introduction
PCOS is a common endocrine disorder in women exhibiting characteristics ranging from hyperandrogenic to metabolic phenotypes, more prevalent in people

of African/Caucasian and Asian ancestry, respectively. Since PCOS impairs fertility without diminishing in prevalence, it was discussed as an evolutionary paradox. GWAS identified 17 SNPs with different allele frequencies, depending on ethnicity, in various susceptibility loci (*FSHR, LHCGR, DENND1A, THADA, C9ORF3, YAP1, HMGA2, RAB5B/SUOX, INSR, TOX3, and SUMO1P1*). The aim of this study was to analyze *in silico* the PCOS phenotype–genotype relationship using these SNPs for analysis of genetic clustering and distance, two measures of the degree of similarity of genetic data.
Methods
HapMap and HGDP databases (hapmap.ncbi.nlm.nih.gov; www.hagsc.org/hgdp/files.html) were used as source of allele frequencies of the 17 SNPs, using data from 622 male and female individuals of various populations, grouped in Africans, Americans, European-Caucasians, Mediterranean-Middle Easterns, Central Asians, Oceanians and East Asians. Genetic clustering was calculated from SNPs data by Bayesian analysis using the STRUCTURE software (burn-in = 5000/50000 MCMC reps; iterations = 20; $2 < K < 10$). The inferred ancestry of individuals was matched with PCOS phenotype data of each group, extracted from a previous meta-analysis. The measure of genetic distance was plotted against the geographic distance between the populations.
Results
The 622 male and female individuals were assigned to five genetic clusters, matching with different world regions (Kruskal–Wallis/Dunn's post-test; $P < 0.0001$), and converging in only two main PCOS phenotypes (Anova/Bonferroni post-test; $P < 0.0001$). The overall genetic distance, calculated using PCOS markers, increased along with the geographic distance among the populations (linear regression; $r^2 = 0.2106$; $P < 0.0001$), in a phenotype-unrelated manner.
Conclusions
Phenotype–genotype correlations were demonstrated for PCOS, suggesting that its genetic gradient results from genetic drift together with intralocus sexual conflict rather than natural selection of phenotypic traits in females. Recognizing the genetic background may be important for the correct pharmacological approach to PCOS treatment.

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P645

How to estimate insulin resistance in PCOS patients: HOMA-IR or QUICKI?

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Insulin resistance affects 50–70% of women with polycystic ovary syndrome (PCOS).
The aim of our study was to estimate the prevalence of insulin resistance by different methods in a single cohort of 63 PCOS patients diagnosed by the Rotterdam criteria.
Methods
Anthropometric measurement, examination and fasting blood tests were made on the 3–5th days of their periods. HOMA-IR (cut off >2.5) and QUICKI (cut off <0.357) was used to assess insulin resistance.
Results
Insulin resistant (IR) patients represented 48 and 65% of the cohort based on HOMA-IR (HIR) and QUICKI (QIR), respectively. Compared to insulin sensitive (IS) patients, IR patients were older (25.5 ± 5 vs 30 ± 6 years, $P < 0.05$). The BMI was similar in the HIR (35.5 ± 7.33 kg/m^2) and QIR (33.15 ± 7.81 kg/m^2) and similar BMI was detected in IS patients according to HOMA (HIS, 25.7 ± 4.74 kg/m^2) or QUICKI (QIS, 25.18 ± 4.53 kg/m^2). Fasting glucose levels did not differ in betwen IR groups (HIR: 4.88 ± 0.51; QIR: 4.88 ± 0.53 mmol/l), but fasting insulin levels were higher in HIR (18.09 ± 8.05 mIU/l) compared to QIR (15.64 ± 7.78 mIU/l) patients. Lipid profiles and HbA1c did not differ significantly between IR groups. The LH:FSH ratio was higher in IR (HIR: 2.89 ± 1.44, QIR: 2.73 ± 1.55) than in IS groups (HIS: 2.11 ± 1.12, and QIS: 2.38 ± 1.21). Patients in IR groups had higher free androgen index (FAI) than IS patients (HIR: 8.64 ± 6.4, QIR: 8.48 ± 6.21, HIS: 6.34 ± 4.4, and QIS: 5.47 ± 3.17). OGTT was performed in 37 patients indicating neither diabetes nor IFG.
Conclusion
By using QUICKI we found more IR patient than with HOMA. Fasting insulin levels and BMI were lower in the QIR than in the HIR group. The FAI was similarly elevated in the IR groups, and was lowest in the QIS group. We suggest that QUICKI detects IR earlier than HOMA.

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P646

BMP15 gene dosage as a relevant X-linked determinant of ovarian development and function

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The X-linked genes accounting for the determination of the ovarian function are still undefined. In the last few years, a large interest has been dedicated to the BMP15 gene. BMP15 gene encodes for a TGFβ-like growth factor of oocyte origin with a critical role in female fertility in mammals and several other species. This gene maps to a locus on the short arm of X chromosome were locates several traits of TS, including ovarian failure. Several missense variations have been identified and experimentally proven as 'loss-of-function' in the BMP15 signaling in animal models and humans. In women, BMP15 mutations occur frequently in association with primary or secondary amenorrhea in the setting of POI. Here, we studied the first variant identified in the BMP15 mature peptide causing the aminoacidic change R329C. By performing western blot, flow-cytometry analysis and a BMP-responsive luciferase-reporter assay on a human granulosa cell line, we evidenced a significant decreased secretion of the mature protein and a time-dependent intracellular accumulation of the precursor in presence of this mutation. Accordingly, the luciferase-reporter assay showed an impaired biological activity of the mutant on granulosa cells, with co-transfection experiments of WT and mutant BMP15 consistent with haploinsufficiency as pathogenic mechanism (similarly to previously reported BMP15 variants in humans and sheep). A concomitant analysis of 40 TS patients by array-CGH and FISH, permitted also the identification of a duplication of the only BMP15 gene in one 45,X patient with spontaneous menarche. The analysis of the rest of the cohort also revealed the presence of a mosaicism level with the euploid cell line $>10\%$ (providing a double copy of BMP15 gene in significant fractions of cells) only in the other 5 TS patients with spontaneous menarche. All other 34 TS patients with primary amenorrhea had only one copy of BMP15 gene in their genome. In conclusion, inactivating mutations of BMP15 can predispose to POI with haploinsufficiency as the main mechanism contributing to the ovarian failure whereas a double dose of BMP15 would be sufficient to partially overcome the deficiency of other X-linked genes. An adequate BMP15 gene dosage would be required for the determination of an adequate ovarian reserve, thus further supporting BMP15 as the first X-linked ovary-determining gene.

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P647

A sensitive method for estrogen profiling in human serum by liquid chromatography–tandem mass spectrometry

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Estrogens are important for the development of the adult female phenotype and are intracellular mediators of androgen effects in many tissues. Measuring several estrogenic compounds in blood or other body fluids may be helpful for the assessment of estrogen status. Liquid chromatography–tandem mass spectrometry (LC–MS/MS) is a versatile technique, which allows for the measurement of conjugated and unconjugated steroids in a single sample volume without derivatization. We used 300 ml of human serum for the analysis. Sample processing was robotized (Hamilton STAR) and included protein precipitation with acetonitrile and liquid–liquid extraction with ethylacetate–heptane. The samples were analyzed on a Waters Acquity UPLC system connected to a Waters Xevo TQ-S tandem mass spectrometer. The compounds were separated on a C-18 column (50×2.1 mm, 1.7 mm particle size), which was developed by gradient elution over 11.5 min, using an aqueous solution of ammonium hydroxide and methanol as mobile phases. 17β-estradiol, 17α-estradiol, ethinylestradiol, estrone, estrone sulfate and DHEA-S were detected in negative ion MRM mode, while progesterone was detected in positive mode. Two product ions were monitored for each compound to check for interferences. Limits of quantification were in the lower picomolar range and total imprecision was $<10\%$. The method was virtually free from ion suppression. In conclusion, we have developed a

sensitive method for the determination of multiple estrogens (endogenous, synthetic, unconjugated, and conjugated) in a single run. The method has been used to analyze several hundred samples from men and fertile and postmenopausal women.

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P648

Metabolic fingerprint of serum in first trimester of healthy pregnancy permits the prediction of macrosomia

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Macrosomia is associated with pregnancy complications and is suggested to predict child's and mother's health. High birth weight (>4,000 g) has been associated to the risk of several major chronic diseases in future life including diabetes, cardiovascular disease or cancer. Additionally delivery of a large baby carries a risk of perinatal complications. The aim of this study was to obtain serum fingerprints of healthy pregnant women to identify early biomarkers of macrosomia and to understand the mechanisms leading to abnormal fetal growth not related to mother's BMI or presence of GDM.

Study was performed on serum samples collected at 12th–14th gestational week from 48 pregnant women (20 with high (HBW) and 28 with normal (NBW) birth weight). Samples were fingerprinted by LC-QTOF-MS and level of adipocyte fatty acid binding protein (A-FABP) enzyme in each sample was measured with ELISA kit. Statistical analysis was performed to find differences between metabolic profiles of women who deliver NBW or HBW neonates. Metabolites were also correlated with the level of A-FABP and birth weight.

We found that low levels of phospholipids, lysophospholipids and monoacylglycerols; low vitamin D3 metabolites but high bilirubin levels were associated to fetal macrosomia at delivery. The level of A-FABP in the serum of the mother (in 12th−14th week of gestation) is positively correlated with the birth weight of the neonate and negatively correlated with the level of serum lipids. Alteration in lipid metabolism during pregnancy put women at risk to develop such diseases like cancer, cardiovascular diseases, type 2 diabetes, or obesity. Enhanced transport of lipids by A-FABP from the mother to the fetus could provoke negative effects on fetal pancreatic β-cells being responsible for future diabetes development in individuals with high birth weight.

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P649

Mineral balance, parathormone and vitamin D in patients with policystic ovary syndrome

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Introduction

Recent data showed that PCOS is related to abnormal calcium and phosphate metabolism. The patients are characterized by elevated levels of PTH and decreased levels of vitamin D. Abnormalities in mineral homeostasis are related to insulin resistance. In this study, we assessed a complex of calcium and phosphate metabolism indices in patients diagnosed with PCOS.

Material and methods

60 women, aged 25±5 years diagnosed with PCOS according to Rotterdam criteria were included to the study. The control group consisted of 22 healthy women and was age (28±5 years) and BMI matched.

Calcium and phosphorus were measured in serum and in 24 h urine collection, the fractional urine excretion was assessed. We also measured the 25OH-vitamin D3, PTH, gonadotropins, estradiol, testosterone, and lipid fraction concentrations. Serum insulin and glucose concentrations were used to calculate the HOMA index.

Results

Total serum calcium levels were higher in PCOS patients (2.4±0.1 vs 2.2±0.1 mmol/l, $P=0.05$) but were within normal range. The other mineral concentrations and urine exertion were the same in both groups and within normal limits. HOMA and estradiol were positively correlated in PCOS group with serum calcium levels and fractional phosphorus excretion was negatively influenced by testosterone concentration in control group. PTH correlated inversely with serum calcium and vitamin D3 in both groups. Insulin and HOMA were correlated positively with vitamin D3 concentrations in PCOS women.

Conclusions

For the first time we showed that patients with PCOS has normal urinary excretion of calcium and phosphorus and that in healthy patients phosphorus excretion is influenced by androgens. We confirmed the link between vitamin D and insulin resistance in patients diagnosed with PCOS.

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P650

Relevance of estrogen activating STS and inactivating SULT1E1 enzymes and estrogen receptors α/β in patients with advanced ovarian cancer

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Background

By regulating the concentration of active estrogens in tumor cells, steroid hormone-inactivating estrogen sulfotransferase (SULT1E1) and estrogen activating steroid sulfatase (STS) may influence the progression of EOC. Therefore, we determined the expression and prognostic impact of both enzymes together with the ERα/β and the progesterone receptor (PGR) in this tumor entity.

Methods

The mRNA expression levels of STS, SULT1E1, ERα/β, and PGR were assessed by quantitative RT-PCR and in a large and well-described advanced stage EOC patient cohort ($n=194$). Protein abundance was determined by immunohistochemistry using an automated quantitative microscopic image analysis system (TissueFAXS, TissueQuest). mRNA and protein levels were correlated with each other and with clinicopathological parameters. Finally, the prognostic values of these inactivating or activating enzymes and the hormone receptors were determined.

Results

Multiple Cox regression analysis showed a significant independent impact of ERα mRNA expression on overall survival (HR=0.87; 95% CI 0.78–0.96), while STS, SULT1E1 as well as ERβ did not have an independent impact on overall- or progression free survival. Remarkably, STS mRNA levels were significantly higher in EOCs from premenopausal women ($P=0.008$). Immunohistochemical analysis showed that ERα was associated with STS ($P=0.002$) and SULT1E1 ($P=0.030$) levels in EOC tumor tissue. A significant correlation was also observed between high STS and high SULT1E1 abundance ($P=0.021$). However, no association was seen between STS, SULT1E1 and PGR. In contrast to ERα, ERß was mainly undetectable in EOC tissue.

Summary and conclusion

In patients with advanced stage EOC, the high levels of ERα, STS and SULT1E1 indicate the importance of estrogen signalling in this tumor entity. This warrants further investigations on the role of the estrogen homeostasis as a target for therapeutic intervention in EOC.

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Copeptin in polycystic ovary syndrome

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Background
Polycystic ovary syndrome (PCOS) is according to the Rotterdam criteria defined as minimum two of: oligomenoré, hyperandrogenism and polycystic ovary. These criteria do not take into account PCOS' association with the metabolic syndrome (MES) and ischaemic heart disease (IHD). Recently we grouped PCOS- patients into four phenotypes depending on normal/high BMI and insulin resistance (IR). We demonstrated that PCOS-patients with high BMI and increased IR had a metabolic phenotype with elevated hsCRP, PAI-1 and thrombin generation time, which are all associated with MES and IHD. Vasopressin mediates water retention, vasoconstriction and ATCH-secreation in healthy. Copeptin is part of the precursor vasopressin peptide and released during processing. It is stable and easy to measure, making it a surrogate marker for vasopressin. Elevated levels of copeptin are associated with IHD, diabetes, microalbinuria and it is hypothesized to be due to central stimulation coursed by low-grade inflammation. Our aim was to study copeptin in PCOS.
Methods
Cross sectional observation study. 98 women with PCOS, age 18–54, no medication for 6 weeks prior, no diabetes. Copeptin was measured using commercial sandwich immunoassay, BRAHMS.
Results
Copeptin was divided into tertiles and increasing levels were associated with increasing levels of C-peptide, free testosterone and PAI-1. Univariate linear regression analysis showed that age ($\beta = -0.21$; $P = 0.036$), C-peptide ($\beta = 0.34$; $P = 0.001$), HOMA (insulin) ($\beta = 0.21$; $P = 0.041$), free testosterone ($\beta = 0.25$; $P = 0.012$), SHBG ($\beta = -0.27$; $P = 0.007$) and PAI–1 ($\beta = 0.27$; $P = 0.008$) correlate with concentrations of copeptin. Multivariate linear regression analysis showed that C-peptide and free testosterone were independently associated. No correlation was found regarding the four phenotypes, BMI, android fat, BP, hsCRP, creatinin, hirsutism score, ovary volume, menstruation cycle or cholesterol.
Conclusion
Copeptin levels in these PCOS-patients demonstrate a association with hyperandrogenism (free testosterone), IR (C-peptide) and low-grade inflammation (PAI-1). The data support the emerging opinion that the Rotterdam criteria do not fully describe PCOS.

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P652

Inverse relationship between hSHBG affinity for testosterone and hSHBG concentration revealed by surface plasmon resonance

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Introduction
Testosterone circulates in the blood mainly bound to albumin and human sex-hormone-binding globulin (hSHBG). It is generally admitted that only the protein unbound fraction of testosterone (free hormone hypothesis) is biologically active. From our routine SHBG binding assay, we observed that SHBG concentration may have an influence on its affinity for testosterone (personal data). To further explore this assumption we used surface plasmon resonance (SPR, Biacore) technic.
Methods
The immobilization of testosterone derivative on the sensorchip CM5 through an oligoethylene glycol linker introduced at the position C-4 was performed by a standard amine coupling. For different plasmas with hSHBG concentrations ranged from 4.4 to 680 nmol/l, an estimation of the equilibrium affinity constant of hSHBG for T (Ka_{SHBG}) was obtained by a kinetic analysis from a set of sensorgrams at different analyte concentrations associated with a curve-fitting of these data.
Results
When the total hSHBG concentration was used to perform the fit to the Langmuir 1/1 model or to the heterogeneous ligand model, the measured Ka_{SHBG} decreased from 1.0×10^{10} to 1.7×10^{8} l/mol or from 2.0×10^{10} to 2.2×10^{7} l/mol respectively, when the total hSHBG plasma concentration increased from 4.4 to 680 nmol/l. This inverse relationship between Ka_{SHBG} and concentration was significant for both models: $r = 0.88$, 0.72 and 0.66 for K_A, K_{A1}, and K_{A2} providing respective P values 1.3×10^{-12}, 6.9×10^{-7} and 1.1×10^{-5} for Langmuir and heterogeneous ligand model.
Comments
These unexpected results suggested that allosteric effects may modulate the hSHBG binding affinity for testosterone. These findings challenged the paradigm which assumes that each SHBG dimer binds two testosterone molecules with similar binding affinity, and questioned the validity of current recommendations for calculating free testosterone for evaluating androgen disorder in humans.

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P653

Evaluation of hormonal pattern and index of oxidative stress in normal weight women with polycystic ovary syndrome

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It is well known that insulin resistance (IR) is associated with polycystic ovary syndrome (PCOS). Oxidative stress (OS) is, in turn, related to IR, with a vicious cycle. PCOS patients presented higher circulating concentrations of oxidative stress products such as homocysteine, malondialdehyde, an increase of superoxide dismutase and reduction of antioxidants such as glutathione and paraoxonase-1 activity. Most studies however concerned obese PCOS subjects. The physiopathology of normal weight PCOS is more complex, even if IR is reported in such situation.
In order to investigate parameters of OS in normal weight PCOS and the relationships with hormonal and metabolic parameters, we have evaluated the concentrations of coenzyme Q_{10} (CoQ_{10}), a component of mitochondrial respiratory chain, also endowed with antioxidant properties, in plasma of PCOS patients ($n = 7$, age 20–25 years, mean BMI 24.8 ± 2.6) and normal menstruating women ($n = 7$, age 20–25 years, mean BMI 22.0 ± 2.5). Also malondialdheyde (MDA), a product of lipid peroxidation, was evaluated. CoQ_{10} levels were determined by HPLC according to Takada *et al*. and MDA levels were determined spectrophotometrically at 535 nm by TBARS assay. Hormonal studies included evaluation of: TSH, fT_3, fT_4, IGF1, testosterone, DHEAS, androstenedione (by CLIA method) and HOMA index.
We did not find a significant difference in MDA (in PCOS patiens mean $\pm$ ES: 7020 ± 2474 pmol/ml vs 12380 ± 2198.9 in controls) and CoQ_{10} (577.2 ± 41.6 pmol/ml vs 495.6 ± 38.8).
PCOS patients showed a trend toward a lower fT_3 levels (2.8 ± 0.07 vs 3.3 ± 0.12 pg/ml) and higher IGF1 levels (303 ± 9.3 vs 279.2 ± 46.1 ng/ml).
These preliminary data suggest that OS is not simply related to IR in normal weight PCOS but there is a complex interplay between hormones influencing follicular growth. They need to be extended to furnish further insight into the mechanisms of hyperandrogenism in such a condition and to give a rationale for a therapeutic employment of antioxidants in PCOS.

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P654

Ovarian steroid cell tumor not otherwise specified with virilizing manifestations: clinical case

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Introduction
Steroid cell tumors are rare ovarian sex cord-stromal tumors with malignant potential comprising <0.1% of all ovarian tumors. A subtype called not otherwise specified (NOS) accounts for approximately one-half of all ovarian steroid cell tumors. The average age of presentation is 43 years, with androgenic clinical features in 56–77% of cases.
Case report
A 21-year-old female, on liver transplantation waiting list due to Niemann–Pick disease, was referred to an endocrinology appointment in November 2013 for hirsutism and acne with 6 months of evolution and progressive worsening. Male pattern baldness, acne, severe hirsutism and clitoromegaly were noticed on physical examination. Laboratory workup revealed: total testosterone 15.89 ng/ml (0.04–0.8), free testosterone 34.74 pg/ml (<2.57), androstenedione >10 ng/ml (0.3–3.3), 17-hydroxyprogesterone 3.5 ng/ml (0.2–1.8), and DHEA-S 16 μg/dl (35–4300. During ultrasound study in August 2013 a right adnexal mass was noted leading to an MRI, which revealed a large 6.4×5.2×5 cm ovarian mass, with normal adrenal glands. Tumor markers were negative. The patient underwent surgery: a small amount of ascitic fluid was evacuated and right salpingo-oophorectomy was performed. No other alterations on the abdomino-pelvic cavity were found. Histopathological examination revealed an ovarian steroid cell tumor NOS, with some features increasing the risk of malignancy (tumor diameter >7 cm, mitotic activity, hemorrhage). Peritoneal fluid was negative for malignancy. Three weeks after surgery androgen level became normal and acne improved.
Conclusion
Androgen-producing tumors should be suspected in women with virilization and high testosterone levels. Approximately one third of steroid cell tumors NOS are malignant, 6% are bilateral and little is known about their behaviour. This case is significant because of the rarity of these tumors in a young age. In this patient a close surveillance is required due to the perspective of hepatic transplantation and immunosupressive therapy in the short term.

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P655

Dietetic Therapy aimed to restart menstrual period in patients affected by anorexia nervosa in weight recovery

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Anorexia Nervosa (AN) is a severe eating disorder characterized by significantly low body weight and fear of gaining weight. Amenorrhea is a very frequent feature in AN and it could persist after normalization of BMI. A well-represented fat mass and an adequate body composition (BC) are necessary for resumption of periods. Patients affected by AN, although in the remission phase, fear of becoming fat and refuse to gain weight. In our study we evaluated the effect of a normocaloric 30% fat diet on BC in patients with AN in weight recovery and its effects in resuming menstrual cycles. Twelve patients were studied: six (group 1) with AN and hypothalamic amenorrhea matched with six (group 2) healthy controls homogeneous for age, body weight and BMI. The following laboratory tests were performed: FSH and LH basal and after GnRH stimulation, oral glucose tolerance test, fT_3, fT_4, TSH, cortisol, 17β-estradiol, 17OH progesterone, testosterone, DHEAS, SHBG, vitamin D and PTH. All subjects underwent BIA and DEXA. Group 1 was on 30% lipids diet regime for 6 months. The content of adipose tissue in the group 1 was significantly underrepresentated ($P=0.02$) and, after 6 months of diet therapy, the fat mass level was increased ($P=0.03$). Furthermore GnRH stimulated FSH levels decreased and LH levels significantly increased ($P=0.05$). Insulin levels after oral glucose tolerance test were significantly decreased at time 90′ and 120′ ($P=0.01$ and $P=0.049$) compared to the baseline. In two of six amenorrhoeic patients spontaneous menstruations restarted. The increase of fat mass obtained after 30% fat diet regime improved hormonal levels and reduced insulin resistance. It should be essential to study the effects of dietotherapy in the long term and increase our study-population.

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P656

Valuation of fat tissue distribution in young women with polycystic ovarian syndrome

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Introduction
Nowadays polycystic ovarian syndrome (PCOS) appears to be one of the most common endocrine disorders that involves from 5 to 10% of women of reproductive age, reaching 75% in the structure of endocrine infertility. Furthermore the distribution of adipose tissue in android region correlates with the prognosis of diabetes, metabolic syndrome and cardiovascular diseases development.
Aim of the study was to determine the type of obesity and to distinguish the characteristic features of it in women with PCOS.
Materials and methods
The study included 35 women suffering from PCOS (according Rotterdam criteria), 27 healthy women composed control group (statistically comparable). Besides the broad analyses of blood hormone levels, mechanical measuring of body volumes, applying exclusion criteria, all patients have undergone dual-energy X-ray absorptiometry (DXA) 'total body' for body composition data.
Results
Hormone spectrum of PCOS patients was characterized by increased LH:FSH ratio (>2.5), testosterone levels, free androgen index, decreased sex hormone-binding globulin (SHBG) level. Progesterone confirmed absence of ovulation. BMI, hip circumference, waist-to-hip ratio didn't differ in groups. Data got from DXA showed total amount of fat in grams, trunk fat amount in grams, gynoid region fat content was not statistically significant. However this parameter in percentage, fat content in android region, android:gynoid ratio in percentage statistically differed in PCOS patients ($P<0.05$).
Conclusion
Data of the study show PCOS patients have abdominal fat distribution. They demonstrated wider waist circumference (77.1±11.2 cm), higher percentage of total fat amount (37.9±3.0%) than in control group ($R=0.846176$; $P<0.05$). Furthermore LH and SHBG levels strongly correlated with total fat amount ($R=0.820996$; $P<0.05$ and $R=0.90006$; $P<0.05$ respectively). PCOS turned to be a multidisciplinary disorder that deserves particular attention of doctors and patients worldwide.

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P657

Serum leptin concentration in gestational diabetes

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Introduction
Gestational diabetes mellitus (GDM) has been recognized as a significant risk factor for metabolic syndrome. Emerging evidence suggests that leptin, an adipocyte-derived hormone, may have independent direct effects on both insulin secretion and action, in addition to its well documented effects on appetite and energy expenditure. The aim of this study was to evaluate fasting serum leptin concentration and its association to insulin resistance in women with gestational diabetes mellitus.
Materials and methods
65 women with GDM and 22 healthy pregnant women (controls) were enrolled. Demographic and clinical data, lipid and carbohydrate metabolism, serum concentration of fasting leptin, insulin, and homeostatic model assessment index were compared and their relationships were analyzed. Metabolic syndrome prevalence was calculated by WHO and NCEP–ATPIII definitions.

Results
The serum leptin level was significantly higher in women with GDM than in the control group ($P=0.04$). There was significant differences between insulin and homeostatic model assessment index and leptin in women with GDM ($r=0.314$, $P=0.02$).
Conclusion
Our data demonstrated that GDM is associated with greater insulin resistance than observed in normal pregnancy and it might be a risk factor for GDM in pregnant women. However, larger prospective cohort studies are needed to confirm the etiologic importance of hyperleptinemia in pregnancy.

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P658

High resolution mass spectrometry to study hormonal regulation of cervical mucus proteome during the menstrual cycle

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The chemical composition of the cervical mucus (CM), its physical characteristics and the volume secreted show cyclical changes during the menstrual cycle.
Clinical proteomics has recently developed new technologies and bioinformatics useful in identifying molecular markers of physiology and pathology. The development of novel mass spectrometers, like the LTQ-Orbitrap, considerably contributed to increase the quantity of acquired data. Aim of the present study was to firstly apply this methodological approach to CM in order to study the effect of hormonal regulation of CM composition, in the various phases of the menstrual cycle.
CM samples of a fertile woman were obtained before, during, and after ovulation. Proteomic analysis was performed by an Ultimate 3000 Nano/Micro-HPLC apparatus coupled with an LTQ-Orbitrap XL hybrid mass spectrometer. Bionformatic tools were used to identify and annotate the proteins according to the gene ontology molecular function system.
Protein identification criteria resulted in the identification of 32 proteins in the pre-ovulatory sample, 48 proteins in the ovulatory sample and 90 proteins in the post-ovulatory sample.
Antioxidant proteins and proteins involved in enzyme regulation resulted significantly increased after the ovulatation; binding proteins were significantly increased at ovulation. Eleven common proteins were identified in all samples. We moreover identified two exclusive proteins in pre-ovulatory phase CM, 16 exclusive proteins in ovulatory phase CM and 50 exclusive proteins in post-ovulatory CM.
This is the first application of high-resolution MS-based proteomics for the identification of protein constituents of CM. This approach might contribute to identify putative biomarkes of the female reproductive tract in fertility and in female infertility.
These data suggest that the major synthesis of proteins in CM is induced some days after ovulation and might be the consequence of the effect of progesterone-induced proteic synthesis in CM.
Bioinformatic functional analysis of proteomic data offered novel informations about the hormonal regulation of CM functions during the menstrual cycle.

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P659

ThyrART: a prospective study on thyroid function and autoimmunity during ovarian stimulation for IVF

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Introduction
The evidence of the impact of OS for IVF and thyroid function or autoimmunity is inconclusive, based mainly on assessments just before and after OS. The aim of this study was to closely monitor the changes on thyroid function and autoimmunity throughout OS for IVF.
Description of methods/designs
In a prospective, interventional study, a flexible GnRH-antagonist protocol was applied to 42 women undergoing IVF ((classic or ICSI), with initiation according to follicular size and estradiol (E_2) concentrations. All women were assessed five times during OS (day 3 of menstrual cycle, day 5 of menstrual cycle, day of hCG administration, oocyte pick-up (OPU) day and day of pregnancy test (15 days after OPU)). Assessment included thyroid function tests (TSH, fT_3, and fT_4) and autoimmunity (anti-TPO, and anti–Tg).
Results
Women had a median (inter-quartile range) age of 36 (6) years, BMI 22.6 (4.8) kg/m^2 and baseline mean ($\pm$S.E.M.) TSH 1.82 ± 1.55 μIU/ml, fT_3 3.37 ± 0.05 pmol/l and fT_4 1.30 ± 0.03 ng/dl. A significant increase was recorded in TSH concentrations between OPU day and the day of the pregnancy test ($P=0.017$), whereas anti-TPO concentrations were decreased ($P=0.043$). No changes were recorded in fT_3 and fT_4 concentrations throughout OS.
Conclusion
This study demonstrated that OS can influence thyroid function and this influence is reflected in TSH concentrations, 15 days after OPU. As the threshold for TSH concentrations for the first trimester of pregnancy is particularly low (<2.5 μIU/ml), special care, such as universal baseline screening and levo-thyroxine supplementation in selected cases, have to be considered in women undergoing OS for IVF.

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P660

Spontaneous fertility and pregnancy outcome in 321 women with Turner syndrome

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Introduction
Turner syndrome (TS) is a chromosomal aberration with a total or partial loss of one of the two X chromosomes, occurring in 1/2000–1/2500 newborn girls. Primary ovarian insufficiency is a classic feature of this syndrome. Therefore, fertility preservation is proposed to girls or adolescents with TS. So far, no pregnancy has been reported in TS women after ovarian or oocyte freezing. The aim of our study was to evaluate the prevalence and the outcome of spontaneous pregnancies in a large cohort of women with TS.
Patients and methods
We recruited 321 TS adult patients from a network of specialised centres in rare diseases (CMERC). Clinical patient's characteristics, reproductive history, hormonal data and karyotype have been collected, after informed consent, in a database (CEMARA). Reproductive data from the French general population have been obtained from French General Health Services (DGS).
Results
Seventeen patients (5.3%) had a total of 32 pregnancies. The two factors correlated with occurrence of a spontaneous pregnancy, were spontaneous menarche and mosaic karyotype (12/17). Pregnancy outcomes were miscarriage ($n=11$), medical interruption ($n=1$), legal abortion ($n=2$) and delivery at term ($n=17$). One pregnancy is still ongoing. Caesarean section rates were higher than in the general population, respectively 59 vs 21% ($P<0.001$). In our cohort, three patients presented pregnancy-induced hypertension, two had preeclampsia. No dilatation or dissection was observed. Two cases of TS were identified in daughters issued from this cohort.
Conclusion
Our study illustrates that spontaneous pregnancy in women with TS is a rare event (5.3%) but patients and their family should be informed before choosing fertility preservation. Higher risks of maternal complications and potential chromosomal abnormalities in children should be mentioned. Prospective studies are necessary to display prognostic values of pregnancy and thus better target fertility preservation programs.

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P661

Mood disturbances in women with polycystic ovary syndrome

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Mood disturbances accompanying the symptoms and hormonal abnormalities are important, but underestimated, in polycystic ovary syndrome (PCOS). Our objective was to assess psychological features in women with and without PCOS.
Materials and methods
We investigated 116 PCOS women (according to the Rotterdam criteria) and 81 healthy control women in Vilnius city (Lithuania) in 2009–2011. Levels of anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS). The 14 items in the HADS (seven for anxiety and seven for depression) were given a score from 0 to 3 with a total score for either depression or anxiety ranging from 0 to 21. A score of 11 or above indicated anxiety and/or depression. We analyzed data of 194 women (114 PCOS and 80 healthy women) who completed the HADS. We tested total testosterone, sex hormone-binding globulin (SHBG), fasting glucose, insulin and lipid profile and calculated free androgen index (FAI) and insulin resistance index (HOMA–IR). Body mass and waist circumference were measured. Modified D Ferriman and J D Gallwey scale was used to assess hirsutism.
Results
Anxiety rate was higher in PCOS women compared to controls (37.7 vs 20.0%, $P=0.006$). 7.9% of PCOS and 10.0% of healthy women showed elevated HADS depression scores, while 5.3% of PCOS women and 1.2% of controls scored above the cutoff values for both subscales indicating anxiety and depression. PCOS women with anxiety were more hirsute (hirsutism index 8.00 ± 5.71 vs 5.63 ± 4.16, $P=0.024$) and had higher HOMA-IR (3.67 ± 3.12 vs 2.82 ± 2.80, $P=0.047$) compared to PCOS women without mood disturbances. Body mass, waist circumference, testosterone, SHBG, FAI and lipid profile did not differ between PCOS women with anxiety and without mood disturbances.
Conclusion
Anxiety is more prevalent in patients with PCOS compared to healthy women and might be associated with hirsutism and insulin resistance.

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P662

Demographic characteristics and therapeutical management in patients with primary ovarian insufficiency

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Introduction
Primary ovarian insufficiency (POI) is commonly defined as amenorrhea or disordered menses for at least 4 months in association with menopausal FSH levels in women who are $<$ 40 years old.
Methods
The aim of our study is to describe the etiology, demographic characteristics, therapeutical management and repercussion in reproduction in patiens with POI. We carried out a retrospective observational study including 25 women with a primary ovarian insufficiency diagnosis after normal pubertal development. We determined different variables such as age at onset of clinical manifestations, etiology, family history, evolution of the disorder after diagnosis, hormonal replacement, time between diagnosis and initiation of treatment and gestational history.
Results
The mean age at onset of clinical manifestations was 32.24 years (S.D. $\pm$ 7.5). Four patients (16%) had autoinmune ooforitis; two patients (8%) had structural abnormalities in the X-chromosome and in 19 patients (78%) the etiology was unknown. 42% of patients with idiopatic etiology had family history. Two patients had spontaneus recovery after the diagnosis, in all other patients the condition was permanent. 35% of patients with permanent ovarían insufficiency did not have hormonal replacement and those who were taking treatment had a delay of more than 1 year between diagnosis and initiation of treatment. 52% of patients were nulliparous before diagnosis. 58% of these patients have used assisted reproduction techniques (ART).
Conclusion
According to literature, idiopatic is the most frequent etiology of POI in our sample and there is evident family association in these patients.
There is an important delay between diagnosis and initiation of hormonal replacement in these patients, probably due to lack of knowledge of this condition of physicians.
We note higher prevalence of POI in the 4th decade. It is important to consider this aspect at the time of recommending the use of ART to avoid unnecessary delays that may increase gestational risks.

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P663

Plasma adhesion molecules concentrations in women with type 1 diabetes mellitus and polycystic ovary syndrome

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Introduction
Polycystic ovary syndrome (PCOS) and type 1 diabetes (T1DM) are accompanied by an increased risk of cardiovascular complications. The higher prevalence of PCOS in T1DM was reported and thus T1DM women with PCOS exhibit a higher risk of cardiovascular diseases. Soluble E-selectin (sE-selectin) and intercellular adhesion cell molecule-1 (sICAM-1) are considered as an early markers of atherosclerosis.
Aim
We aimed to evaluate plasma levels of sE-selectin and sICAM-1 in T1DM women with PCOS (T1DM+PCOS) and in age-matched, BMI-matched women with PCOS without diabetes (PCOS) and T1DM without PCOS (T1DM–no PCOS). We also estimated the relation of studied adhesion molecules with clinical and phenotypic parameters.
Study participants and methods
We studied 37 women with T1DM – ten women with T1DM+PCOS and 17 women T1DM–no PCOS, 33 women with PCOS, and 15 healthy women (control group). The clinical examination, concentrations of plasma sE-selectin, sICAM-1, hormonal profile and ultrasonographic evaluation of ovaries were performed in all women. Insulin sensitivity in T1DM was calculated using estimated glucose disposal rate (eGDR).
Results
Plasma concentrations of sICAM-1 and sE-selectin did not differ between all groups and were positively associated with adiposity measures in studied groups. In entire T1DM group we found a relationship of sE-selectin and sICAM-1 with eGDR ($r=-0.468$, $P=0.013$ and $r=-0.536$, $P=0.003$) and sE-selectin with HbA1c ($r=0.445$, $P=0.019$). sE-selectin correlated with insulin dose in T1DM+PCOS ($r=0.790$, $P=0.006$) and in T1DM–no PCOS ($r=0.519$, $P=0.032$). In T1DM+PCOS sE-selectin was related to the number of ovarian follicles ($r=0.762$, $P=0.01$). In PCOS the association of sICAM-1 with the follicle count ($r=0.449$, $P=0.018$) was observed.
Conclusion
T1DM+PCOS women do not exhibit higher concentration of adhesion molecules and present similar associations between adhesion molecules and clinical parameters in comparison to studied groups. The observation about relation of adhesion molecules with follicle count in T1DM+PCOS and PCOS group requires further study.

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P664

The relationship between serum lipocalin-2 levels and insulin resistance in patients with PCOS

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Introduction
Lipocalin-2 is abundantly expressed in mature adipocytes and causes insulin resistance. In the physiopathology of PCOS, insulin resistance has great importance. The purpose of this study was to determine serum lipocalin-2 levels in patients with PCOS and to investigate its relationship with body fat percentage, hs-CRP and insulin resistance.
Methods and designs
This study was planned as a case controlled study. We enrolled 44 women with PCOS and 47 healthy women in the study. Fasting serum glucose, insulin, lipocalin-2, free testosterone, and hs-CRP levels of all the women included in the study were measured and body fat percentages were calculated. Insulin resistance of the individuals was calculated by the HOMA–IR formula and insülin sensitivity by the QUICKI formula.
Results
There was no significant difference between the two groups in terms of age and BMI ($P > 0.05$). Serum lipocalin-2, hs-CRP, free testosterone, insulin levels and HOMA–IR were determined as significantly high in the patients with PCOS ($P < 0.05$). Furthermore, body fat percentage was determined statistically significantly high in PCOS patients ($P = 0.02$). In the correlation analysis, no relation was determined between lipocalin-2 and insulin resistance and insulin sensitivity. A significant positive correlation was determined between free testosterone, hs-CRP and body fat percentage with lipocalin-2.
Conclusion
As a result, in our study, lipocalin-2 was found to be increased in women with PCOS and any relation between serum lipocalin-2 level and glucose metabolism was not determined. Besides, we think that, serum lipocalin-2 level in women with PCOS might be an indication of increased cardiovascular diseases.
Keywords
Lipocalin-2, PCOS, insulin resistance.
Running head
Lipocalin-2 and PCOS.
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P665

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

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Bone morphogenetic protein 8 (Bmp8) is important for postnatal gonad functions. Targeted depletion of either Bmp8a or Bmp8b has been shown to cause male infertility due to the degeneration of germ cells. However, no direct signaling pathway of BMP8 has been clarified *in vitro* due to the lack of functional BMP8 proteins. Of interest, we found that Bmp8 transcripts are not only abundant in the rat testis but also in the ovary. Therefore, we aimed to unveil the BMP8 downstream and characterize its functions in the ovary. Firstly, we generated recombinant BMP8 proteins and found that the bioactive BMP8 proteins mediate the BMP signaling by promoting the phosphorylation of Smad1/5/8. Over-expression of either ALK3 or AKL6 in cells enhances the BMP8 signaling, indicating they are the type 1 receptors of BMP8. In addition, shRNA knockdown experiments demonstrated that ACVR2A and BMPR2 can serve as the type 2 receptors for BMP8. Using a rat superovulation model, we found that Bmp8 transcripts can be upregulated by the LH signaling. Microdissection in combination with mRNA quantification indicated that Bmp8 is mainly located in the cumulus cell–oocyte complex. Treatment with recombinant BMP8 *in vitro* significantly induced expansion of the cumulus cell–oocyte complex isolated from preovulatory follicles. Taken together, these results suggest that BMP8 may promote female fertility by inducing cumulus cell expansion through the Smad1/5/8 pathway.

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P666

Does polycystic ovary syndrome influence incidence nonalcoholic fatty liver disease in women?

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The aim was to assess associations among metabolic abnormalities in polycystic ovary syndrome (PCOS) and NAFLD.
Materials and methods
In 184 women with PCOS and 125 healthy premenopausal volunteers sex steroids, lipids, glucose, insulin, aminotranspherases, CRP, free androgen index (FAI), HOMA and E_2:testosterone were calculated. Hepatic steatosis was determined by ultrasound. The analysis of multivariate (logistic regression) due to the presence of NAFLD among both groups (141 with NAFLD and 168 without NAFLD) was preformed. For the analysis introduced: BMI, waist circumference, WHR, testosterone, SHBG, FAI, E_2:testosterone, AST, ALT, LDL-C, HDL-C, TG, CRP, glucose, insulin, HOMA, and PCOS.
Results
56.7% of PCOS women had NAFLD while women without PCOS had NAFLD in 49.6%. PCOS–NAFLD women had higher BMI, WHR and waist circumference compared to women with PCOS without NAFLD and women without PCOS. PCOS-NAFLD women had lower SHBG, E_2/T ratio and higher FAI compared to other groups. ALT levels were higher in PCOS-NAFLD women than in other groups. PCOS women with and without NAFLD had higher fasting glucose, insulin and HOMA-IR than women without PCOS. PCOS women had higher TG and lower HDL-C than women without PCOS. Logistic regression showed that all of the analyzed factors influence NAFLD but BMI > 25 kg/m^2, $E_2/T < 80$, ALT > 19 IU/l, and glucose > 85 mg/dl were independent factors.
Conclusions
NAFLD is more common in women with PCOS than in women without PCOS. PCOS affects the development of NAFLD in women, but is not independent factor. Hyperandrogenism in PCOS may increase the risk of NAFLD indirectly by obesity, insulin resistance, and directly by the hepatotoxic effect.

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P667

Increased prolactin levels cause increased MPV in women with PCOS

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Introduction
It is well known association between cardiovascular disease and PCOS. Approximately 17–43% of women with PCOS have hyperprolactinemia. Increased levels of prolactin often associated with an increased risk for thromboembolic events, but underline pathophisiological mechanism still unknown. The strong association between hyperprolactinemia and platelet aggregation is well known. Platelets play a key role in the development of atherothrombosis, a major contributor of cardiovascular events. Mean platelet volume (MPV) is a marker of platelet size that reflect to activity of the platelet. MPV is easily determined on routine hemogram analysis at a relatively low cost. Larger platelets with higher MPV values are hemostatically more reactive and produce higher amounts of the prothrombotic factor.We also investigated the relationships between serum PRL levels and MPV levels in subjects with PCOS.
Designs and methods
We conducted consecutively subjects with PCOS who have higher prolactin levels ($n = 72$) and who have normal prolactin levels ($n = 207$) and subjects without PCOS ($n = 90$).
Results
MPV levels were significantly higher in PCOS subjects with elevated prolactin levels compared to both in PCOS with normal prolactin levels and control groups

($P<0.001$). MPV levels were positively correlated with prolactin levels ($r=0.387$, $P<0.001$), free testosteron levels ($r=0.135$, $P=0.010$) and negatively correlated with platelet counts ($r=-0.333$, $P<0.001$). Furthermore, multiple regression analysis showed that prolactin levels were directly related to MPV levels ($R^2=0.239$, $\beta=0.354$, $P<0.001$).

Conclusions

In the present study we showed that increased prolactin levels cause increased MPV levels in PCOS and results of multiple regression analysis showed that prolactin levels were directly effected to MPV levels independent from other factors. This implies a higher risk of hypercoagulability and therefore an increased risk of future cardiovascular disease in pcos subjects wiht eleveted prolactin levels.

Keywords

PCOS, prolactin, MPV.

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Growth hormone IGF axis – basic

P668

Effects of partial deficiency of IGF1 on hepatocellular architecture

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Background

IGF1 is mainly produced in the liver and it induces beneficial effects on many systems. However, the role of IGF1 on the liver itself is poorly understood, probably due to the fact that healthy hepatocytes barely express IGF1 receptors. Previous works in our group showed that IGF1 supplementation induces beneficial actions in cirrhosis, inducing a relevant histological improvement, reducing fibrosis[1]. Based on these data the aim of this work was to inquire into the mechanisms of IGF1 in development of liver architecture using a novel murine model of partial deficiency of IGF1 without other exogenous damage[2].

Materials and methods

Livers from heterozygous ($Igf1^{+/-}$) 5 months old mice (Hz, $n=10$) were compared to those from homozygous $Igf1^{+/+}$ (WT, $n=10$, same age) by assessing hepatic gene expression (by microarray and further quantitative PCR) of cytoskeleton, cellular junctions, and extracellular matrix proteins. The effect of the replacement therapy with low doses of rhIGF1 (2 µg/100 g Bw per day, for 10 days, s.c.) was evaluated in parallel (group Hz+IGF, $n=10$, same age). Complementarily, histological studies were performed.

Results

Compared to controls, Hz mice showed a significant alteration of genes encoding proteins of the cytoskeleton and hepatocellular junctions which appear to cause abnormal hepatic architecture, as it was asseverated by histological studies, showing misalignment of hepatocyte cords. An abnormal gene expression of liver extracellular matrix was also observed in Hz mice. IGF1 replacement therapy normalized liver morphology and improved gene expression of many of these factors.

Conclusion

The mere IGF1 deficiency lead to an increase in liver vulnerability by modifying the expression of hepatic genes involved in the morphogenesis of the live and IGF1 replacement therapy normalizes these findings improving the hepatocellular architecture.

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P669

Mechanism of hepatoprotection derived from IGF1 replacement therapy

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Background

IGF1 is mainly produced in the liver and it induces beneficial effects on many systems. However, the role of IGF1 on the own liver is poorly understood, probably due to the fact that healthy hepatocytes barely express IGF1 receptors. Previous works in our group showed that IGF1 supplementation induces beneficial actions in cirrhosis, including antioxidant, anti-inflammatory and antifibrogenic effects. Based on these data the aim of this work was to deep into the mechanisms of IGF1 in hepatoprotection using a novel murine model of partial deficiency of IGF1 without previous pathology[1].

Materials and methods

Livers from heterozygous ($Igf1^{+/-}$) 5 months old mice (Hz, $n=10$) were compared to those from homozygous $Igf1^{+/+}$ (WT, $n=10$, same age) by assessing hepatic gene expression (by microarray and further quantitative PCR) of IGF1-related factors, antioxidant enzymes, inflammatory response molecules, heat shock proteins and cell death markers. The effect of the replacement therapy with low doses of rhIGF1 (2 µg/100 g Bw per day, for 10 days, s.c.) was evaluated in parallel (group Hz+IGF, $n=10$, same age). Complementarily, the marker of oxidative damage malondialdehyde (MDA), was measured.

Results

Firstly, we confirmed that the reduced *Igf1* gene expression correlated with low circulating levels and interestingly IGF1 replacement therapy restored *Igf1* gene expression suggesting a novel role of IGF1 in autoregulation. Compared to controls, Hz mice showed an increased hepatic lipid peroxidation, overexpression of genes related to pro-inflammatory pathways, hypoexpression of antioxidant enzymes and apoptosis inhibitory factors genes. IGF1 supplementation normalized lipid peroxidation and improved gene expression of majority of these factors.

Conclusion

All these data together suggest that IGF1 deficiency increases liver vulnerability to oxidative damage and offer the possibility to develop new therapeutic strategies using IGF1 as a hepatoprotective factor.

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P670

Young female with acromegaloid features, pituitary macroadenoma, and an uncomplicated pregnancy

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Thirty-two years old female G2P1A0 seen at our endocrinology clinic 9 years ago complaining of persistent menstrual irregularities associated to elevated prolactin values. MRI done revealed a pituitary microadenoma. However, she refused treatment for microprolactinoma. Four years afterwards, patient return complaining of recurrent episodes of headache. Repeated MRI showed a pituitary macroadenoma, so start on cabergoline treatment.

Once more, patient was lost to follow-up and on 2012 she visited our clinic at 24th weeks of gestation with history of progressive hands and feet enlargement. On physical examination marked prognathism, hands and feet enlargement, acanthosis nigricans and hirsutism were found, so acromegaly was suspected. Elevations of prolactin and IGF1 levels were found during whole pregnancy.

After 6 months *post-partum*, laboratories were repeated and basal and 2 h insulin showed marked elevation, increased HOMA index, and normal IGF1 and GH values. Thus, the diagnosis of insulin mediated pseudoacromegaly was confirmed.

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P671

Epigenetic regulation of GH target genes and its relation to *in vivo* GH signaling in skeletal muscle of adult human males: a pilot study

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Background
GH secretion and action change with age in adult human subjects, and this play an important role in substrate metabolism in aging subjects. Targeted disruption of the GH receptor in mice extends longevity, and this is associated with decreased expression of apoptosis-related genes including caspase-9 (CASP9) in skeletal muscle.
Aim
To study DNA methylation of putative GH target genes in skeletal muscle of adult male subjects in relation to body composition, physical fitness, serum IGF1 levels and *in vivo* GH signaling.
Subjects and methods
In this pilot study we included 12 healthy adult subjects (ten males and two females) subdivided into a 'young' group ($n=5$) and 'old' group ($n=7$) (mean $\pm$ S.E.M. age: 24 ± 2.7 vs 25.6 ± 2.0). Total and phosphorylated STAT5b were measured by WB at $t=30$ min, and IGF1 and *SOCS/CIS* gene expression at $t=120$ min. by RT-PCR in skeletal muscle following an i.v. GH bolus. In the GH-unstimulated state DNA methylation in muscle tissue was measured by Infinium HumanMethylation450 BeadChip technology (Illumina, CA, USA). We did a hypothesis-free analysis of the methylation level of each CpG locus in the 450k array comparing 'old' ($n=7$) vs 'young' ($n=5$) We focused on CpG loci located within 1500 and 200 bases upstream transcription start sites (TSS200 and TSS1500) increasing the possibility that the CpG site is regulating the gene transcription.
Results
Following the GH bolus significant STAT5b phosphorylation and gene expression of IGF1 and SOCS/CISH were recorded in all subjects with no significant difference between the two groups. Taking the false discovery rate into account the *CASP9* gene methylation was statistically significant with an adjusted P value <0.05, while the mean beta-difference was only 0.011 being fully unmethylated in the 'young' group.
Conclusion
i) Significant activation of GH signaling in terms of pSTAT5b and expression of canonical target genes are detectable *in vivo* in skeletal muscle of adult human male subjects without a distinct impact of age, ii) methylation of the promotor region of CASP9 were increased in older subjects indicative of epigenetic modification; and iii) this *in vivo* model holds promises to disclose hitherto unrecognized regulatory mechanism of GH activity.

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P672

Demographic and clinical characteristics and treatment patterns of polish acromegalic patients switched to lanreotide AUTOGEL 120

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Objective
The aim of the study was to examine characteristics and treatment patterns of Polish acromegalic patients.
Methods
A retrospective database analysis was conducted. Adult acromegalic patients treated medically for ≥1 year including at least three injections of lanreotide AUTOGEL 120 were recruited in 36 centres between 29/10/2010 and 31/03/2012. Descriptive analysis was performed to describe demographic and clinical characteristics, treatment history and disease control. Biochemical control was defined as GH ≤2.5 mg/l.
Results
A total of 143 patients were included, mean age (S.D.) of 51.4 years (14.0) and mean BMI 29.4 (S.D. 6), 71.3% female, coming from 36 centres in different Polish regions. The most commonly reported symptoms of the disease were headache (84% of patients) and arthralgia (82% of patients). Comorbidities included: hypertension (60.1%), diabetes (33%), and gall stones (21.7%). Macroadenoma was present in 79% of patients, microadenoma – in 16.1%, the mean tumor size was 19.1 mm (S.D. 12.2). Hyperprolactinemia was found in 16% of cases. 74.8% of patients had undergone pituitary surgery, 18.8% received external radiotherapy. In the moment of inclusion, the mean time since surgery/radiotherapy was 7.3/7.7 years respectively. 83% patients were treated with octreotide LAR before switching to lanreotide AUTOGEL 120. As additional treatment 28 patients (20%) received bromocriptine, 11 patients (7.7%) – cabergoline and 10 (7%) – pegvisomant. Owing to concomitant pituitary insufficiency in 67 patients (47%) levothyroxine ($n=57$), hydrocortisone ($n=46$), desmopressine ($n=5$) and sex hormones ($n=30$) were used. 54% of patients with GH data ($n=101$) achieved biochemical control of their disease. In the population of patients receiving octreotide LAR 30, then lanreotide AUTOGEL 120, mean interval between subsequent doses was 4 weeks for octreotide and 5 weeks for lanreotide.
Conclusions
The study population represents a wide cross-section of acromegalic patients – their demographic and clinical characteristics under the conditions of the health care in Poland.

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P673

Incidence and late prognosis of acromegaly in Denmark: preliminary data

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Introduction
Acromegaly is a rare disease caused by GH hypersecretion from a pituitary adenoma. However, accurate estimates of incidence and prevalence are scarce and not based on nationwide populations. It is well known that surgical cure may normalize mortality and improve morbidity but similar data are not available for patients receiving medical treatment.
Method
We first validated the ICD-8 and ICD-10 diagnosis codes for acromegaly in The National Registry of Patients by a systematic patient chart review of related diagnosis and pertinent clinical biochemistry. Data on the entire acromegaly cohort were then obtained by individual patient chart review and by using several national databases such as The Cancer Registry, The Registry of Cause of Death and The National Registry of Patients.
Results
The mean incidence rate of acromegaly from 1989 to 2010 were 3.8 cases/million per year (95% CI 3.6–4.1) with a prevalence of 85 cases/million in 2010. The mean age at diagnosis was 47 years (95% CI 46–48) with a sex distribution on 49% males (95% CI 45–53). We found a 1.4 (95% CI 1.2–1.7)-fold increased mortality among patients with acromegaly compared to the background population. The impact of different treatment modalities on mortality is under investigation.
Conclusion
This nationwide study is the first to provide accurate estimates of incidence and prevalence rates of acromegaly and to evaluate the impact of medical treatment as compared to surgery.

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P674

Pollution agents contribution in goitrogenous process in dobrogea: the Southeastern boundary of Romania

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Objective
Assessment of the health status in a population from a territory with apparently normal iodine intake may take in consideration the incidence of goiter as a mass pathologic process. Considering goiter as a result of both endogenous and exogenous factors, the study of its incidence and correlations with potentially goitrogens represents a prophylactic medical activity. Use of the term 'paraendemic' for a certain territory does not justify a 'relaxation' of the medical activity concerning the goiter problem.
Materials and methods
Healthy and goitrous inhabitants of Dobrogea region have been examined. The region has been arbitrarily divided into four areas: Seacoast area, Central Dobrogea area, Peri-Danubian area and Tulcea area. The study consisted in the clinical evaluation of thyromegaly, measurement of thyroid volume, assessment of thyroid function, incidence of thyroid autoimmunity and its correlations with gender, age, thyroid volume, place of living, cigarettes smoking, involvement of polluting goitrogen factors and biochemical characteristics of the underground waters.
Results
An increased prevalence of the goitrogen process has been found, with an ascending percentage within the last 14 years. The mean thyroid volume in healthy subjects (13.42 ± 1.2 ml) was minimal in Seacoast area (10.1 ± 40.4 ml) and rose progressively in Peri-Danubian area (15.8 ± 0.7 ml) toward to Tulcea area (17.9 ± 0.8 ml), with differences according to gender and age. The associated functional abnormalities have been represented by increased prevalence of subclinical hypothyroidism (SCHT) (14.6%). TPO-Ab level (representing the thyroid autoimmunity) has been found elevated in the general population (11.1%) and in the hypoechoic goiter bearers (53.5%). A high concentration of polluting goitrogens has been found in Danube and underground water, mostly characterized as intense mineralized water.
Conclusions
Inhabitants from an even limited territory may present significant variations of thyroid structure, volume, and function, with various pathologic consequences.
The relatively high prevalence of non-toxic goiter in a territory without iodine deficit could be correlated to other goitrogen factors like autoimmunity and different polluting agents.

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P675

The etiologies of growth hormone insufficiences: about 170 cases

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The GH deficiency (GHD) may be congenital with or without cause identified or acquired secondary to organic lesion in the hypothalamic region (HH). In all cases a magnetic resonance imaging is necessary.
Aim
Investigate the causes of GHD Population and methodology GHD children were followed at the department of endocrinology. In addition to clinical examination, a testing hypophysiogramme is made with glucagon/propranolol/GH testing insulin on GH/cortisol, IGF1, FT_4, TSH, ACTH, prolactin and urinary density $\pm$ Restriction Test water). The exploration was completed by a pituitary magnetic resonance imaging (MRI) and a molecular study
Results
The GHD is congenital in 84.3% of cases. An interruption of the pituitary stalk syndrome is found in 2/3 of the cases. Cause acquired is gained rare (2.5%). It is represented by a case of radiotherapy and 5 tumoral lesions (4craniopharyngioma, arachnoid cyst). In 13% of cases the GHD is 'idiopathic'.
Congenital GHD is related to molecular abnormalities in 13.7% of cases: Mutation of transcription factors (Prop1n: 14; Pit 1n: 1) and the GHRH-R ($n=7$). no molecular abnormality is found in patients with ectopic neurohypophysis
Discussion and conclusion
'Idiopathic' GHD has become almost exceptional due to the advent of MRI and the development of molecular biology.
The high frequency of malformations anomalies is explained by the method of recruitment of patients, and the insufficiency of organic acquired lesions observed. many practitioners don't know, the effects of chronic illness and/or their treatment, especially intracranial tumors on the somatotropic axis.

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P676

GH replacement therapy affects the morphology and function of the left ventricle in patients with adult-onset GH deficiency

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Background
GH plays an important role in maintaining physiological morphology and function of the left ventricle (LV). In GH deficient (GHD) patients a systolic and/or diastolic LV dysfunction has been documented. LV systolic dysfunction results from reduced LV mass (LVM), which subsequently leads to a decrease of the LV ejection fraction (EF). Results from clinical trials evaluating the effect of GH replacement therapy on the morphological and functional changes of the LV in patients with GHD are controversial.
Objective
The aim of the study was to evaluate the effect of GH replacement therapy on the morphological and functional changes of the LV in patients with GHD.
Methods
Patients with adult-onset GHD were treated with GH. Transthoracic echocardiography was performed at baseline, after 6 and 12 months of the treatment. Interventricular septal thickness (IVST), posterior wall thickness (PWT), left ventricular end-diastolic diameter (LVEDD), left ventricular end diastolic volume (LVEDV), LVM, stroke volume (SV) and LV EF were evaluated at echocardiography and the values at respective time points were compared by a paired *t*-test. In addition, a gender stratified analysis was performed.
Results
45 patients (21 men, 24 women; age 19–61 years) with GHD were included. At 6 months, only increase in PWT ($+0.2$ mm; $P=0.044$) was significantly changes compared with baseline. At 12 months of the replacement therapy, statistically significant increase in LVM ($+8.6$ g; $P=0.035$) and improvement of LV EF ($+1.4\%$; $P=0.005$) were seen.
In men, significantly higher values of IVST, PWT, LVEDD, LVEDV, SV and LVM were found at 12 months of follow-up while no such effect was observed in women.
Conclusion
A mild increase in LVM and improvement of LV EF accompanies long-term GH hormone replacement therapy. The effect on left ventricle morphology is more pronounced in men than in women.

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P677

Positive impact of GH treatment on trabecular bone using grey-level texture analysis

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Introduction
GH deficiency (GHD) is associated with reduced bone mineral density (BMD) and treatment leads to its increase. BMD, a quantitative bone parameter, doesn't bring whole information about bone status. Nowadays, bone quality shows as main determinant of bone strength, fracture prediction and treatment effect monitoring. A method to assess bone quality through the grey-level texture analysis from lumbar spine DXA scan is trabecular bone score (TBS).

Objectives
First, to assess the effect of recombinant human GH (rhGH) on BMD and TBS in GHD adults. Second, to analyse the factors influencing the effect of the therapy on bone.
Methods
A study of hypopituitary adults with GHD after 2 years of replacement treatment in IGF1 normalising regimen. Patients were divided according to gender, onset of GHD and etiology. They were adequately treated for other pituitary axis deficiencies and supplemented with calcium and vitamin D. TBS was derived from DXA scans of L-spine at baseline, month 12 and 24. Bone turnover markers (CTx and Osteocalcin) were evaluated at baseline, months 3, 6,12 and 24.
Results
86 patients were included (mean 34.3 years, 48 males) mostly with GHD caused by surgery ($n=46$). After 2 years 14% ($P=0.001$) increase of L-spine BMD was observed, with higher increase in males ($+16.4\%$, $P=0.001$) and childhood onset (CO) of GHD($+17.1\%$, $P=0.008$). TBS increased 2.3% ($P=0.035$) after first year and 3.1% ($P=0.002$) after second year with higher increase by CO ($+5.02\%$, $P=0.05$) and no difference acording gender. Bone markers increased during the first 12 months of treatment with subsequent decrease of CTx.
Conclusion
Replacement with rhGH led to increase in bone mass and TBS associated with positive changes of bone turnover markers. Gender and onset of the GHD have shown as important predictors of bone microarchitecture resopnse to rhGH replacement.

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P678

Analysis of bioactive IGF-binding proteins by quantitative western ligand blotting in different biological fluids for biomarker research

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IGF binding proteins (IGFBPs) are important biomarkers for diagnostics and treatment studies. In different physiological conditions IGFBPs are actively degraded by specific proteases. Due to the detection of intact and fragmented IGFBPs, ELISA or RIA techniques may generate biased IGFBP-data. We thus developed quantitative western ligand blotting for comprehensive monitoring of intact IGFBPs and IGFBP-profiles in biological fluids of vertebrates. The dynamic range for each IGFBP was determined and signal intensities were quantified by using recombinant standards as calibrators on each blot. Curve fitting was achieved by a four parametric nonlinear regression of each separate IGFBP. Inter- and intra-assay precision for each IGFBP were determined by using spiked samples as quality controls on each blot. Exploratory measurements were performed in plasma and serum of pigs, cattle, mice, sheep, goats, dogs, fishes and humans. Furthermore, cerebrospinal fluid (CSF), follicular fluid (FF) or seminal plasma (SP) were examined in cattle or horse respectively. For all substrates the minimum required dilution for sample loading was determined. IGFBPs were present in all investigated substrates with a species and substrate specific IGFBP profile. Most abundant plasma and serum IGFBPs were IGFBP3, -2 and -4. In SP we were able to quantify comparably high amounts of IGFBP5. In CSF we further identified an IGFBP2 fragment. In CSF and FF both IGFBP2 and IGFBP3 were detected. The lower limits of detection of IGFBP2, 3, and 4 were 0.062, 0.26 and 0.03 ng respectively. The intra- and inter-assay precision in serum and plasma were <15 and $<20\%$ fulfilling the acceptance criteria of recent bioanalytical guidelines. To conclude, the qWLB represents a standardized methodology for measuring IGFBP profile in biological fluids characterized by high reproducibility and sensitivity. QWLB is attractive particularly for translational biomedical research.

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P679

Latest results from the PATRO Adults study of Omnitrope® for the treatment of adult patients with GH deficiency

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Introduction
PATRO adults is an ongoing, international, open, longitudinal, non-interventional study of the long-term safety and efficacy of Omnitrope (Sandoz), a recombinant human GH (rhGH). This study will provide additional data on the long-term safety of rhGH in adult patients with severe GH deficiency (GHD). Here, we present safety data from an interim analysis.
Methods
Eligible patients are male or female adults who are receiving treatment with Omnitrope and who have provided informed consent. Patients treated with another rhGH before starting Omnitrope therapy are eligible for inclusion. 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.
Results
To date (November 2013), 600 patients have been enrolled in the study; 309 (52%) have received previous GH treatment. Mean (S.D.) age of enrolled patients is 50.4 (15.3) years, and mean (SD) BMI is 29.5 (6.4) kg/m^2. So far, 438 adverse events (AEs) have been reported in 157 (26%) patients, with 47 (10.7%, in 29 (5%) patients) regarded as serious. Thirty-nine AEs (8.9%) in 25 (4.2%) patients were suspected as drug-related. These included ten nervous system disorders, eight general disorders/administration site conditions, seven musculoskeletal/-connective tissue disorders and three investigations (increased IGF levels). One serious AE (dyspnoea) in 1 (0.2%) patient was suspected as drug-related. Of the 50 patients who have discontinued treatment, 10 (1.6%) did so due to an AE.
Conclusions
On the basis of this interim analysis, Omnitrope treatment in adults with GHD is well tolerated in a real-life clinical practice setting, both in rhGH-naïve and previously treated patients. The ongoing PATRO Adults study will provide important data on the diabetogenic potential and overall safety of long-term GH treatment in this population.

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P680

Increased relative amount of visceral and subcutaneous adipose tissue in long-lived GH-releasing hormone knockout (GHRHKO) mice; is it beneficial or not?

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Introduction
Long-lived mice with targeted disruption of the GHRH gene (GHRH knockout; GHRHKO) constitute a unique animal model of altered somatotrophic signaling and are characterized by reduced body mass and size, low plasma IGF1 and enhanced insulin sensitivity. These features are also observed in long-lived GH receptor knockout (GHRKO) mice, characterized by increased visceral obesity that usually promotes insulin resistance. GHRKO mice have also increased subcutaneous fat accumulation. Increased amount of subcutaneous adipose tissue may be associated with enhanced insulin sensitivity.

Objectives and methods
The aim of the study was to assess an absolute weight and relative amount (percent of body mass) of visceral (perinephric and perigonadal – epididymal in males or parametrial in females) and subcutaneous fat depots, obtained during visceral or subcutaneous fat removal respectively. This quantification was performed in GHRHKO and normal (N) male and female mice, at ∼ 6–7 months of age.
Results
The relative amount of visceral adipose tissue was increased in both, male and female GHRHKO mice ($P=0.007$, $P=0.044$; 1.53-fold, 1.88-fold respectively) compared to N animals. Also, the relative amount of subcutaneous fat was increased in both, male and female GHRHKO animals ($P<0.001$, $P=0.005$; 3.76-fold, 2.68-fold respectively). There were no differences in absolute weights of either visceral or subcutaneous adipose tissue between GHRHKO and N mice.
Conclusion
The relative amount of visceral and subcutaneous adipose tissue in GHRHKO mice is, as in GHRKO dwarfs, increased. This phenomenon may lead, via reduced somatotrophic signaling characterized for both mutants, to increased insulin sensitivity. Our findings may confirm an important beneficial role of the suppressed GH signaling in lifespan regulation.

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P681

Effects of two mTOR inhibitors on *in-vitro* models of GH-secreting pituitary adenomas

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Background
Gigantism and acromegaly are the main consequences of GH excess, mainly due to a pituitary adenoma. Surgery is the first therapeutic option, but also medical therapy is employed, being represented mostly by somatostatin analogues (SSA), that reduce both tumour mass and GH hypersecretion. However about 10% of patients is resistant to SSA.
PI3K/Akt/mTOR pathway, activated by growth-factors such as IGF1, is important in regulating many cellular processes (viability, apoptosis and cell cycle), and it is deregulated in several neoplasms including GH-secreting pituitary tumours.
Aim of the study
To understand how PI3K/Akt/mTOR pathway can influence viability and GH secretion in pituitary adenomas, we employed two inhibitors (Everolimus, mTOR inhibitor, and NVP-BEZ235, mTOR and PI3K inhibitor), evaluating their effects in presence or in absence of IGF1.
Material and methods
We employed two GH-secreting pituitary adenoma rat cell lines and we assessed cell viability. Culture medium was collected to evaluate GH secretion by ELISA.
Results
Both compounds (10–500 nM) caused a significant reduction in cell viability up to 60% in the two cell lines. On the other hand, IGF-1 induced cell viability by 60% as compared to control cells in GH3 cells and by 40% in GH4C1 cells. This effect was efficiently counteracted in both lines by Everolimus and NVP-BEZ235, indicating that these compounds could act, at least in part, on IGF-1 activated pathways. GH secretion was reduced by IGF1 in both cell lines; this effect was enhanced by Everolimus, but not by NVP-BEZ235 in both cell lines.
Conclusions
Our results suggest that both compounds interfere with IGF1 signalling in GH-secreting rat cell lines, that could be used as a model to identify alternative pharmacological targets for GH-secreting pituitary adenomas resistant to SSA therapy.

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P682

Evaluation of the effect of X chromosome abnormalities on the response to GH therapy in children with turner syndrome

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Introduction
Turner syndrome (TS) is a condition caused by structural or numerical abnormalities of X chromosome. Growth deficiency is characteristic for patients with TS, and particular karyotype abnormalities of the X chromosome may be associated with different responsiveness to human GH (hGH) therapy. The aim of the study was to determine the effect of TS karyotype on growth velocity during hGH therapy in TS.
Methods
23 TS patients treated with hGH with at least 2 years follow-up, were enrolled in a longitudinal observational study. Genetic analyses in order to evaluate the X chromosome structural or numerical abnormalities were performed and patients were categorized as X-monosomy ($n=12$), X-mosaicism with structural abnormalities of the second X ($n=6$), X-mosaicism without structural abnormalities of the second X ($n=4$) and structural abnormalities of the second X ($n=1$). Anthropometric parameters and height velocity (HV) were evaluated annually. Height and HV were expressed as SDS.
Results
In our study the lowest mean HVSDS in the first year of hGH therapy in TS with X-monosomy in comparison to patients with other chromosome abnormalities ($+1.83\pm2.39$ vs $+4.4\pm2.59$; $P<0.002$) was showed. In the second year of therapy the tendency of a lower mean HVSDS in patients with X-monosomy was noted, though without a statistical significance ($P=0.243$). No statistical difference in HVSDS in the first and second year of hGH therapy between patients with X-mosaicism with structural abnormalities of the second X, X-mosaicism without structural abnormalities of the second X and structural abnormalities of the second X were recorded.
Conclusions
X-monosomy determines a poorer growth response during the first year of hGH therapy in TS. The best response to hGH therapy during the first year was observed in TS patients with X-mosaicism with structural abnormalities of the second X.

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P683

The pathophysiology of increased hepatic IGF1 expression in an ovine model of polycystic ovary syndrome

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Exposure of pregnant sheep to increased concentrations of testosterone during midgestation results in a PCOS-like condition in the female offspring that includes increased hepatic IGF1. The aim of this study was to investigate the molecular pathophysiology of this increase. We studied 11-month-old female offspring whose mother had been treated with testosterone propionate (TP: 100 mg) in oil ($n=8$), or oil control ($n=4$) twice weekly from day 62 to 102 gestation. The first experiment was to determine if altered IGF1 was a consequence of prenatally programmed differential gene methylation. We assessed IGF1 CpG methylation using pyrosequencing. There was no IGF1 gene hypomethylation ($P>0.05$) associated with prenatal TP exposure. The next experiment was to assess if the prenatally programmed primary hyperinsulinaemia, resulted in augmented IGF1 through altered GH secretion or action. There was no difference in pituitary GH1 expression ($P>0.05$), number of somatotrophs assessed by immunohistochemistry ($P>0.05$) or serum GH concentrations ($P>0.05$). In addition there were no differences in hepatic GHR ($P>0.05$) or expression of other GH-regulated genes including *HNF6/ONECUT1*, *G6PC* and *SLC2A2* ($P>0.05$). The next experiment was to determine if contemporaneous androgen exposure was involved. The sheep express higher hepatic *AR* as well as having increased capacity for ovarian and adrenal androgen synthesis. We investigated the effects of two weeks of TP (100 mg twice weekly) ($n=5$) or control ($n=5$) on normal female sheep. This regimen did not alter hepatic IGF1 expression ($P>0.05$). To date the pathophysiology of increased hepatic IGF1 in the ovine model of PCOS is unclear. As circulating insulin and hepatic *NR3C1* ($P<0.05$) and *HSD11B1* ($P<0.05$) are increased and both insulin and glucocorticoids can augment STAT5 we now plan to assess intra-hepatocyte signalling pathways. This clinically realistic, prenatally programmed, ovine model can be used increase our understanding of the molecular pathophysiology of metabolic dysfunction in PCOS.

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Male reproduction

P684

The effects of improving testosterone levels on cardiovascular risk markers in young men with idiopathic hypogonadotropic hypogonadism: preliminary findings from a prospective study

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Association between idiopathic hypogonadotropic hypogonadism (IHH) and atherosclerotic disease in young males remains unclear. The present study aimed to determine the effect of improving the testosterone level on cardiovasculary (CV) risk markers in young males with IHH.

Materials and methods

The study included 19 non-obese males with IHH and 17 healthy controls. The patients were treated with hCG therapy ($n=8$) or testosterone replacement ($n=11$). Testosterone levels were targeted within the upper % 50 of normal range. Group 1 included 19 IHH patients who were at visit of first time and 14 IHH patients completed the 3rd month follow-up visit. Control group included 17 healthy subjects. Inflammatory markers, including homocysteine, hsCRP, mean platelet volume (MPV) and lipid parameters were evaluated. Endothelial function – measured via flow-mediated dilation (FMD) of a brachial artery – and carotid intima media thickness (IMT) were evaluated using high-resolution ultrasonography.

Results

There weren't any differences in Group 1 (mean age: 29 years; BMI: 25.1 kg m^2) and control group (mean age: 31 years; BMI: 24 kg m^2) regarding to age and BMI ($P>0.5$, for all). Only, Carotid IMT was higher in Group 1 than the control group with respect to other atherosclerotic risk markers ($P<0.01$, for all).

There was no change at BMI (25.6 kg/m^2) after three months in preliminary findings from our prospective study ($P>0.05$). Carotid IMT was descreased at 3rd month visit, but the difference was not statistically significant ($P=0.059$). And, there was a negative correlation between carotid IMT and free testosterone ($r=-0.43$, $P=0.024$).

Conclusion

If prospective findings from the our present study will show an association between an improved testosterone level and atherosclerotic risk markers it can be say that atherosclerosis could be improved after treatment of IHH in young males.

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P685

An analysis of the possible relationship circulating concentrations of ghrelin, LH, FSH, testosterone and inhibin B at the time of puberty in normal healthy boys

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Ghrelin receptor GHSR1α is expressed in hypothalamo–pituitary–gonadal tissues. Ghrelin reduces GnRH secretion in pre-pubertal period and concentrations of ghrelin are positively correlated with testosterone at adulthood. Nevertheless, the role of ghrelin in affecting pituitary and gonadal functions during normal pubertal development remains elusive. A possible correlation between ghrelin and LH, FSH, testosterone and inhibin B was examined in boys ($n=557$) between 10 and 20 years. Blood samples were collected and plasma concentrations of ghrelin, LH, FSH, testosterone and inhibib B were determined by ELISA. Data were analyzed using Student's *t*-test, ANOVA and Pearson correlation. The concentrations of ghrelin significantly increased at 11th and 14th years, markedly decreased till 16th year, increased significantly at 17th year, suddenly declined to low concentrations at 18th year to be maintained at later years. The concentrations of LH increased to a small peak at 12th year, an intermediate peak at 15th year and a highest peak at 18th year and then declined at 19th year to be maintained at 20th year. The concentrations of testosterone increased progressively till 13th year, abruptly increased to several fold at 15th year, augmented increasingly to reach highest concentrations at 18th year. The concentrations of FSH increased abruptly at 11th year, progressively increased to peak at 15th year and attained 2nd peak at 18th year. The concentrations of inhibin B progressively increased reaching a peak at 14th years and thereafter progressively declined to low concentrations at 20th year. The concentrations of ghrelin, LH, testosterone, FSH and inhibin B increased significantly at mid puberty. The concentrations of ghrelin were maintained, the levels of LH, testosterone and FSH continued to rise and the concentrations of inhibin B declined at late puberty/adolescence. In conclusion, the concentrations of ghrelin, LH, FSH, testosterone and inhibin B were positively correlated at early and mid puberty.

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Semen quality in patients with newly diagnosed non-Hodgkin lymphoma

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Objective

To analyse the semen quality in patients with newly diagnosed non-Hodgkin lymphoma before starting the treatment.

Materials and methods

We evaluated semen quality in 29 patients with non-Hodgkin lymphoma who underwent sperm banking in our clinic over a 9-year period. Semen samples were collected by masturbation after 2–7 days of sexual abstinence. Age at banking, semen volume, sperm concentration, and total and progressive sperm motility were recorded. Semen parameters were compared to established World Health Organisation (WHO) reference values (WHO Laboratory Manual for the Examination and Processing of Human Semen, Fifth Edition, 2010).

Results

The median age of the patients was 28 years (range 18–42); median semen volume was 2.0 ml (range 0.6–3.5); median sperm concentration was 52×10^6 per ml (range 1.0–269); median total and progressive sperm motility were 31 (range 0–83) and 27% (range 0–50) respectively. According to the reference values of the WHO 6 of 29 patients (20.7%) in this series had a semen quality within the normal range, and 23 of 29 patients (79.3%) had abnormal semen quality. 17 patients (58.6%) had single damage (all patients in this group had asthenozoospermia) and six patients (20.7%) had combined damages (oligoasthenozoospermia).

Conclusion

Patients with non-Hodgkin lymphoma have an increased risk for inadequate semen quality before any treatment. In our study, 79.3% of these men had abnormal semen quality according to the WHO reference intervals for values of semen parameters. Generally, patients with newly diagnosed non-Hodgkin lymphoma need counselling about their reproductive function and semen cryopreservation should be considered before undergoing gonadotoxic treatment.

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Hypogonadism in aged hospitalized male patients: prevalence and clinical outcome

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Objective

Male hypogonadism is common in the elderly and has been associated with increased risk of mortality. Our objective has been to assess the prevalence of primary and central hypogonadism in elderly male patients admitted to the hospital because of acute illness. We also evaluated the relationships between gonadal dysfunction and in-hospital mortality.

Patients and methods

150 male patients, aged $\geq$65 years, admitted during 2010 and 2011 in our geriatric unit, were studied. Serum concentrations total, bioavailable and free testosterone, as well as of FSH, LH were quantified in every patient. Hypogonadism was defined by the presence of serum testosterone levels lower than 200 ng/dl.

Results

Hypogonadism was found in 80 patients (53.3%). Serum gonadotropin concentrations were elevated in 43.7% of these patients, where as 41.3% of hypogonadic patients showed normal and 15% low gonadotropin concentrations. Respiratory tract infection and congestive heart failure were the main cause of

hospitalization in hypogonadal men, whereas acute cerebrovascular disease was the main reason for admission in eugonadal patients. From the 13 patients who died during hospitalization, 12 were hypogonadic. Patients who died showed significantly lower serum levels of total, free and bioavailable testosterone than those found in patients who survived.
Conclusion
Our results show that about half of male patients admitted for acute illness have hypogonadism, mainly of non-hypergonadotropic type. Gonadal hypofunction is significantly related with in-hospital mortality. A low value of serum testosterone may be a predictor for mortality in elderly male patients.

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P688

Is elevated red blood cell distribution width a new risk factor for polycystic ovary syndrome?

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Objective
The red blood cell distribution width (RDW) is being recognized as a global marker of chronic inflammation, high level of oxidative stress, and cardiovascular disease risk. We aimed to investigate the relation between the level of RDW and highly sensitive C-reactive protein (hs-CRP), insulin resistance, BMI and body fat percentage in women with polycystic ovary syndrome (PCOS).
Methods
Cross-sectional study of 90 PCOS (2003 Rotterdam Consensus Conference criteria) and 87 normal women, age and BMI-matched. Complete blood counts, fasting serum glucose, serum insulin, hs-CRP, lipids, and free testosterone levels were measured. The homoeostasis model assesement of insulin resistance (HOMA-IR) index was calculated.
Results
RDW levels were significantly higher in the PCOS group compared with the control group (12.98 ± 0.92 vs $12.59 \pm 0.84\%$, $P = 0.004$). There was a relation between RDW level and BMI, body fat percentage, hs-CRP and insulin resistance. In logistic regression analysis, high level of RDW was determined as an independent risk factor for the development of PCOS (OR = 2.08, 95% CI = 1.18–3.67, $P = 0.011$). However, in multiple regression analysis, insulin resistance, hs-CRP level, BMI and body fat percentage were found to have no effect on RDW level.
Conclusions
In our study, the level of RDW was a risk factor for the development of PCOS, independent from insulin resistance, hs-CRP and free testosterone levels. For this reason, elucidating the mechanism of higher RDW levels in women with PCOS can provide additional information about pathophysiology of PCOS.
Key Words
PCOS, RDW, hs-CRP, insulin resistance.

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Analysing by decade, testosterone undecanoat depot injectable does not increases prostate volume: study during up to 6 years on hypogonadic patients

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Aim
Re-analyzing the effect of injectable testosterone undecanoat depot (TUD) in hypogonadic patients.
Materials & methods
(A) Patients: at onset 191 men with hypogonadism (median age: 64 years). (B) Distribution: by decade. (C) TUD (Nebido^{R}-Bayer-Schering) 1000 mg was injected one per 3 months i.m. (D) Prostate volume (PV) by per-abdominal ultrasound: 3.5 MHz probe, elliptical volume (cm^3), Aloka 550. (E). Time of analysis: before starting testosterone (T0), after ½ month (T1), 3 (T2), 6 months (T3), 1 (T4), 2 (T5), 3 (T6), 4 (T7), 5 (T8), 6 years (T9). (F). Maximum increment percent from T0 was noted Δ M %. Average increment was noted Δ A %. G. Statistical analysis: Student's *t*-test.
Results
i) All average prostatic volume for decade will be presented. ii) PV at T0 increases with age, from 17.33 (19–29 years) to 47.41 (80–89 years), $P = 0.0007$. iii) Inside a specific decade no significant increased in PV was registered (all $P > 0.05$), excepted 80–89 decade (at 3 and 4 years: $P < 0.002$). iv) In some patients, especially from 50 to 79 years, TUD could decrease slightly prostatic volume. v) When withdrawing the treatment, PV increased. vi) Five patients 78–89 years died after 1 year after withdrawing the treatment.
Conclusions
Considering the risk for prostate (in elderly), testosterone undecanoat 1000 mg depot injectable is a safe treatment, even after 3–6 years of administration. Precautions should be accorded to men over 80 years old, after the third administration. Further observation needed.

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The variant *FSHB* −211G>T attenuates serum FSH levels in the supraphysiological gonadotropin setting of Klinefelter syndrome

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Background
Klinefelter syndrome (KS) is the most frequent genetic cause of male infertility. Individuals share the endocrine hallmark of hypergonadotropic hypogonadism, displaying high gonadotropin levels due to deficient testicular function. A single-nucleotide polymorphism (SNP) located within the *FSHB* promoter region (−211G>T, rs10835638) was recently shown to be associated with reduced serum FSH levels and other reproductive parameters in men. The objective of this study was to analyse the impact of *FSHB* −211G>T on endocrine and reproductive parameters in untreated and testosterone-treated KS patients.
Subjects & methods
Patients were retrospectively selected from the clientele attending the Department of Clinical Andrology, Centre of Reproductive Medicine and Andrology, University Clinics Münster, a tertiary-referral centre, for couple infertility and andrology. A total of 316 non-mosaic KS individuals between 18 and 65 years were included while excluding higher-grade aneuploidies or mosaic form. Subjects were genotyped for *FSHB* −211G>T by TaqMan assay. Associations of the single-nucleotide polymorphism genotypes with endocrine and reproductive parameters were assessed.
Results
The untreated group comprised 253 men, in which the *FSHB* −211G>T T-allele was significantly associated with reduced serum FSH levels (−4.6 U/l per T-allele, $P = 7.7 \times 10^{-3}$). TT-homozygotes displayed 50% lower mean and median FSH levels compared to GG-homozygotes. A non-significant and less pronounced gradient for reduced LH levels over the three genotypes was also observed. Testosterone treatment ($n = 154$) abolished the observed association on FSH levels. When analysing patients before and under testosterone treatment ($n = 91$) gonadotropin levels were similarly suppressed independently of the *FSHB* genotype.
Conclusions
A hypergonadotropic setting such as KS does not mask the genotype *FSHB* −211G>T effects on FSH serum levels. The impact was even more pronounced when compared to normal or infertile men, while gonadotropin suppression under testosterone treatment seems to be independent of the genotype. Thus the *FSHB* −211G>T genotype is a key determinant in the regulation of gonadotropins. pathopyhsiologies.

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Clinical correlates of enlarged prostate size in subjects with sexual dysfunction

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Introduction
Digito-rectal examination (DRE) of the prostate is provides useful information on the state of prostate growth and on the presence of suspected peripheral nodules. The aim of this study is to describe the clinical and biochemical correlates of finding an enlarged prostate size at DRE in subjects with sexual dysfunction (SD).
Methods
A consecutive series of 2379 patients was retrospectively studied. The analysis was focused on a subset of subjects ($n=1823$; mean age 54.7 ± 11.4) selected for being free from overt prostatic diseases. Several parameters were investigated.
Results
After adjusting for confounders, the presence of an enlarged prostate size at DRE was associated with a higher risk of metabolic syndrome (HR $=1.346$ (1.129–1.759); $P=0.030$), type 2 diabetes mellitus (HR $=1.489$ (1.120–1.980); $P=0.006$), increased LDL cholesterol (>100 mg/dl; HR $=1.354$ (1.018–1.801); $P=0.037$) and increased mean blood pressure values (HR $=1.017$ (1.007–1.027) for each mmHg increment; $P=0.001$). Accordingly, enlarged prostate size was also associated with a higher risk of arteriogenic erectile dysfunction (ED), as well as with other andrological conditions, such as varicocele and premature ejaculation. PSA levels were significantly higher in subjects with enlarged prostate size when compared to the rest of the sample (HR $=3.318$ (2.304;4.799) for each log unit increment in PSA levels; $P<0.0001$). Arteriogenic ED, according to different criteria, was also associated with increased PSA levels.
Conclusions
Our data support the need to examine prostate size either by clinical (DRE) or biochemical (PSA) inspection in subjects with SD, in order to have insights into the nature of the SD and the metabolic and cardiovascular background of the patient.

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Clinical implications of measuring prolactin levels in males of infertile couples

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Introduction
Although in females of infertile couples abnormal PRL has a definitive role in the medical flow-chart, its role in males is less clear. Animal models suggest that PRL does not play a major role in male reproduction, although its trophic action on male accessory glands was often observed. Studies in humans are scanty. We systematically evaluated possible clinical and ultrasound correlates of PRL in males of infertile couples.
Methods
Out of 288 consecutive males of infertile couples, 269 (36.6 ± 4.4 years) without genetic abnormalities were studied. All men underwent physical, biochemical, seminal evaluation and scrotal and transrectal ultrasound before and after ejaculation. Ejaculatory and erectile functions were assessed by PEDT and IIEF-15, respectively; prostate-related symptoms by NIH-CPSI and IPSS; psychological symptoms by MHQ.
Results
Among semen parameters, only the positive association between PRL and ejaculate volume was significant, even adjusting for age, total testosterone and TSH (adj.$r=0.126$, $P<0.05$). In a logistic ordinal model, adjusting for the aforementioned confounders and ejaculate volume, PRL was negatively associated with delaying ejaculation according to PEDT#1 score (Wald $=4.65$, $P<0.05$). In an age- and ejaculate volume-adjusted, iterative binary logistic model, low PRL was associated with a fivefold risk of any failure in controlling ejaculation (HR $=5.15$ (1.15–23), $P<0.05$). Among scrotal and transrectal ultrasound features, we found a significant positive association between PRL and seminal vesicles (SV) volume and inhomogeneity, before and after ejaculation, and with deferential ampullas diameter. Associations with PRL were confirmed in nested 1:1 case–control analysis. No significant associations were found between PRL and other clinical parameters.
Conclusions
For the first time, this study extends the concept of a trophic effect of PRL on male accessory glands from animals to humans. We report a positive association among PRL and ejaculate and SV volume, before and after ejaculation. Low PRL is associated with a lessened ability to control ejaculation.

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Seminal, ultrasound and psychobiological parameters correlate with metabolic syndrome in male members of infertile couples

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Introduction
Metabolic syndrome (MetS) is a diagnostic category which identifies subjects at high risk for diabetes and cardiovascular diseases, erectile dysfunction (ED) and male hypogonadism. However, MetS impact on male infertility has been poorly studied. We systematically evaluated possible associations between MetS and clinical characteristics in men with couple infertility.
Methods
Out of 367 consecutive subjects, 351 men (36.0 ± 8.0 years) without genetic abnormalities were studied. MetS was defined according to the International Diabetes Federation and American Heart Association/National Heart, Lung, and Blood Institute classification. All men underwent physical, hormonal, seminal and scrotal ultrasound evaluation. Erectile and ejaculatory functions were assessed by International Index of Erectile Function-15 erectile function domain (IIEF-15-EFD) and Premature Ejaculation Diagnostic Tool (PEDT), respectively while psychological symptoms by Middlesex Hospital Questionnaire.
Results
Out of 351 patients, 27 fulfilled MetS criteria. Among ultrasound features, in an age-adjusted logistic model, only testis inhomogeneity was significantly associated with increasing MetS factors (HR $=1.36$ (1.09–1.70), $P<0.01$). In an age-adjusted model, MetS was associated with a stepwise decline in total testosterone (TT) ($B=-1.25\pm0.33$, $P<0.0001$), without a concomitant rise in gonadotropins. At univariate analysis, progressive motility and normal morphology were negatively related to the number of MetS components (both $P<0.0001$), but when age and TT were introduced in a multivariate model, only sperm morphology retained a significant association ($B=-1.418\pm0.42$; $P=0.001$). The risk of ED (IIEF-15-EFD score <26) increased as a function of the number of MetS factors, even after adjusting for age and TT (HR $=1.45$ (1.08–1.95), $P<0.02$). No association between PEDT score and MetS was observed. Finally, after adjusting for age and TT, somatization and depressive symptoms were associated with increasing MetS components ($B=0.66\pm0.03$, $P<0.05$; $B=0.69\pm0.03$, $P<0.02$; respectively).
Conclusions
In men with couple infertility, MetS is associated with hypogonadism, poor sperm morphology, testis ultrasound inhomogeneity, ED, somatization and depression. Recognizing MetS could help patients to improve not only fertility but also sexual and overall health.

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Seminal, clinical and color-Doppler ultrasound correlations of prostatitis-like symptoms in males of infertile couples

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Introduction
'Prostatitis-like symptoms' (PLS) are a cluster of bothersome conditions defined as 'perineal and/or ejaculatory pain or discomfort and National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) pain subdomain score $\geq$4' (Nickel's criteria). PLS may originate from the prostate or from other portions of the male genital tract. Although PLS could be associated with 'prostatitis', they should not be confused. The NIH-CPSI is considered the gold-standard for assessing PLS severity. Although previous studies investigated the impact of prostatitis, vesiculitis or epididymitis on semen parameters, correlations between their related symptoms and seminal or scrotal/transrectal color-Doppler ultrasound (CDU) characteristics have not been carefully determined. And no previous study evaluated the CDU features of PLS in infertile men.
This study was aimed at investigating possible associations among NIH-CPSI (total and subdomain) scores and PLS, with seminal, clinical and scrotal/-transrectal CDU parameters in a cohort of males of infertile couples.
Methods
PLS of 400 men (35.8 $\pm$ 7.2 years) with a suspected male factor were assessed by the NIH-CPSI. All patients underwent, during the same day, semen analysis, seminal plasma interleukin 8 (sIL8, a marker of male genital tract inflammation), biochemical evaluation, urine/seminal cultures, scrotal/transrectal CDU.
Results
PLS was detected in 39 (9.8%) subjects. After adjusting for age, waist and total testosterone (TT), no association among NIH-CPSI (total or subdomain) scores or PLS and sperm parameters was observed. Yet we found a positive association with current positive urine and/or seminal cultures, sIL8 levels and CDU features suggestive of inflammation of the epididymis, seminal vesicles, prostate, but not of the testis. The aforementioned significant associations of PLS were further confirmed by comparing PLS patients with age-, waist- and TT-matched PLS-free patients (1:3 ratio).
Conclusion
NIH-CPSI scores and PLS evaluated in males of infertile couples, are not related to sperm parameters, but mainly to clinical and CDU signs of infection/inflammation.

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P695

Sexual functioning in patients with end-stage liver disease before and after liver transplantation

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Background
Data on sexual dysfunction (SD) in cirrhotic patients are limited. Our aim was to evaluate the sexual function of patients with end-stage liver disease and to compare it with the results after liver transplant (LT) and with that of a controlled group matched by age and gender.
Methods
Changes in sexual functioning questionnaire were used to evaluate SD in cirrhotic patients awaiting LT and in the post-LT setting 1 year after transplant. Clinical data and a complete set of sexual hormonal profile were obtained. Controls were given the same questionnaires.
Results
58 patients, 69% men, were included and compared to 58 controls. 92% of men presented SD during the waiting period for LT vs 63% of controls ($P<0.01$). In women, of whom 88% were in menopausal stage, SD was present in 94 vs 72% of controls ($P=0.7$). 1 year post-LT 74% of men presented SD ($P=0.09$), while no changes were detected in women. In men, sex hormones showed a pattern of central hypogonadism during the pre-LT period with a decrease in sex hormones (free testosterone in 83%, testosterone in 53%) and normal values of FSH and LH (72 and 81%). Estradiol and prolactin were increased in 86 and 72% respectively. Levels of DHEA-S were decreased in 97% of men. Results one year after LT showed a decrease of prolactin and estrogen to normal levels. There was an increase in testosterone levels ($P=0.05$). Levels of DHEA-S remained low.
Conclusion
SD with central hypogonadism is extremely common in cirrhotic patients awaiting LT. The reduced levels of DHEA, possibly due to adrenal dysfunction, is an aspect that deserves further investigation. LT improves SD in men, demonstrated both subjectively (questionnaires) and objectively (improvement in sex hormone levels).

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Nonalcoholic steatohepatitis as a novel player in metabolic syndrome-induced erectile dysfunction: an experimental study in the rabbit

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A pathogenic link between erectile dysfunction (ED) and metabolic syndrome (MetS) is now well established. Nonalcoholic steatohepatitis (NASH), the hepatic hallmark of MetS, is regarded as an active player in the pathogenesis of MetS-associated cardiovascular disease (CVD). This study was aimed at evaluating the relationship between MetS-induced NASH and penile dysfunction. We used a non-genomic, high fat diet (HFD)-induced, rabbit model of MetS, and treated HFD rabbits with testosterone, with the selective farnesoid X receptor (FXR) agonist obeticholic acid (OCA), or with the anti-TNFα mAb infliximab. Rabbits fed a regular diet were used as controls. Liver histomorphological and gene expression analysis demonstrated NASH in HFD rabbits. Several genes related to inflammation (including TNFα), activation of stellate cells, fibrosis, and lipid metabolism parameters were negatively associated to maximal acetylcholine (Ach)-induced relaxation in penis. When all these putative liver determinants of penile Ach responsiveness were tested as covariates in a multivariate model, only the association between hepatic TNFα expression and Ach response was confirmed. Accordingly, circulating levels of TNFα were increased 15-fold in HFD rabbits. testosterone and OCA dosing in HFD rabbits both significantly reduced TNFα liver expression and plasma levels, with a parallel increase of penile eNOS expression and responsiveness to Ach. Also neutralization of TNFα with infliximab treatment fully normalized HFD-induced hypo-responsiveness to Ach, as well as responsiveness to vardenafil, a phosphodiesterase type 5 inhibitor. Thus, MetS-induced NASH in HFD rabbits plays an active role in the pathogenesis of ED, likely through TNFα, as indicated by treatments reducing liver and circulating TNFα levels (testosterone or OCA), or neutralizing TNFα action (infliximab), which significantly improve penile responsiveness to Ach in HFD rabbits.

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P697

Metformin *in vitro* and *in vivo* increases adenosine signalling in rabbit corpora cavernosa

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Introduction
In subjects with erectile dysfunction (ED) responding poorly to sildenafil, metformin was reported to improve erections.
Aims
To investigate metformin's mechanism of action on erectile function, particularly focusing on adenosine (ADO), and NO signalling in an animal model of high fat diet (HFD)-induced metabolic syndrome (MetS).
Methods
In vitro contractility studies of penile strips. Penile expression of genes related to ADO- or NO-signalling was also evaluated.
Main outcome measure
In vitro contractility studies were used to investigate the effect of *in vivo* and *ex vivo* metformin administration on ADO- or acetylcholine (Ach)-induced relaxation of penile strips from HFD, as compared to animals fed a regular diet (RD).
Results
Expression of ADO receptor type 3 (A3R), ADO deaminase (ADA), AMP deaminase type 1 (AMPD1), and 2 (AMPD2) was decreased in HFD, as compared to RD. Accordingly, in HFD the ADO relaxant effect was potentiated as compared to RD ($P<0.02$). *In vivo* metformin treatment in both RD and HFD significantly increased the ADO relaxing effect ($P<0.0001$, and $P<0.01$ respectively, vs relative untreated groups), although to a different extent. In fact, the IC50/IC50 ratio in RD increased four folds vs HFD (RD IC50 ratio $=13.75\pm2.96$; HFD IC50 ratio $=2.85\pm0.52$). In CC from HFD, *in vivo* metformin i) normalized A3R, ADA, and AMPD1, ii) further decreased AMPD2, iii) increased dimethylarginine dimethylamino-hydrolase (DDAH1), and iv) partially restored impaired Ach-induced relaxation. *Ex vivo* metformin time- and dose-dependently increased the relaxant effect of ADO in RD. The potentiating effect of metformin on ADO-induced relaxation was significantly reduced by pre-incubation with NOS inhibitor L-NAME. Interestingly, *in vivo* testosterone supplementation in HFD rabbits: i) increased penile expression of AMPD2, and ii) restored ADO-induced relation, up to RD level.
Conclusion
Metformin *in vitro* and *in vivo* increases ADO signalling in CC, most probably interfering with ADO breakdown and NO formation.

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P698

Waist circumference and waist-to-height ratio in relation to semen quality and serum reproductive hormones levels among Estonian fertile men

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Introduction
It has been suggested that BMI, especially above 30, is associated with subfertility in men. At the same time validity of BMI to distinguish variability in body composition, have been questioned (MacDonald, 2010). In our study, we employed more accurate surrogate measures of adiposity to investigate the relations of semen parameters and reproductive hormones with waist circumference (WC) and waist-to-height ratio (WHtR).
Methods
During 2010–2011 male partners of pregnant women were invited to participate in this study. A total of 260 men were divided into three groups according to their WC: <94 cm; 94–102 cm; ≥102 cm and into two groups according to their WHtR: <0.5; ≥0.5 (Ashwell, 2011). Semen was collected by masturbation and sperm parameters were analyzed according to WHO criteria. Patient height, weight, WC, and WHtR were recorded. Body composition was determined using TANITA Corporation (TBF-300MA). Blood samples were collected for sex hormones. Data analyses were performed using the SPSS 20.0. Statistical significance was defined as $P<0.05$.
Results
The mean age of the 260 men was 32 years. WC and WHtR were inversely related to testosterone levels. Men with WC ≥102 cm and with WHtR ≥0.5 had lower total sperm count than did men with a WC <94 cm and with WHtR <0.5. WC and WHtR were related neither to estradiol, FSH, and LH levels nor to sperm volume, concentration, motility or morphology.
Conclusions
Our preliminary results suggest that visceral adiposity (as assessed by increased WC above 94 cm and WHtR ≥0.5) is specifically associated with lower testosterone levels. Men with WC ≥102 cm and with WHtR ≥0.5 are also increased risk of lower total sperm count.
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P699

A possible association between circulating concentrations of obestatin, LH, FSH, testosterone and inhibin B during puberty in normal healthy boys

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The G protein coupled receptor of obestatin GPR39 is expressed in pituitary and gonads, indicating its possible role in regulation of pituitary and testicular function. The present study examined a possible association of obestatin with LH, FSH, testosterone, and inhibin B at puberty. Blood samples were collected from 10 to 20 years old boys ($n=557$) and concentrations of obestatin, LH, FSH, testosterone, and inhibin B were determined using specific ELISA. Data were analyzed using Student's *t*-test, ANOVA, and Pearson correlation. The concentrations of obestatin augmented significantly at 11th year, steadily increased reaching peak levels at 17th year and declined at 18th, 19th and 20th year. The concentrations of LH reached a small peak at 12th year, an intermediate peak at 15th year, a highest peak at 18th year. The concentration of testosterone gradually increased till 13th year, increased significantly at 15th year, further increased to peak at 18th year and decreased to slightly low concentrations at 20th year. The levels of FSH increased abruptly at 11th year, progressively increased to a 2nd peak at 15th year, a 3rd peak at 18th year. The concentrations of inhibin B progressively increased to reach highest levels at 14th year and thereafter progressively declined till 20th year. The concentration of obestatin, LH, FSH, testosterone, and inhibin B augmented significantly during mid puberty. Whereas the concentrations of obestatin and inhibin B decreased, the levels of FSH, LH, and testosterone continued to rise during late puberty/adolescent. The concentrations of obestatin, LH, FSH, and testosterone were positively correlated at early and mid puberty, whereas the concentrations of obestatin and inhibin B were positively correlated at all stages of pubertal development. In conclusion, the present study demonstrates a positive correlation between circulating concentrations of obestatin and LH, FSH, testosterone, and inhibin B in boys at mid puberty.

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P700

46 XX male syndrome with hypogonadotrophic hypogonadism: a case report

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Introduction
46 XX male syndrome generally presented as hypogonadotrophic hypogonadism.
Case report
A 39-year-old man was referred to our clinic with a pituitary mass. He had a history of pituitary adenoma of $45\times28\times40$ mm size which was found after his

admission with right-sided vision loss at 2006. The hormonal analyses showed hypogonadotrophic hypogonadism without any excess hormone levels. A transcranial pituitary adenomectomy was performed. Pathology was considered as an adenoma which had no immunstaining with TSH, ACTH, GH, and prolactin. After the operation, his vision loss improved.
When he admitted to our clinic he was suffering from loss of libido, infertility, headaches, and relapsing of vision loss on the right side. Hormonal analyses showed hypogonadotrophic hypogonadism. An MRG of the hypophysis showed a $37\times32\times28$ mm pituitary mass. Second operation was performed at 2011**.** The pathology was negative for any of the immun staining. After the operation there was residual pituitary mass of $24\times25\times20$ mm but the patient had no headaches and vision problems. But loss of libido and infertility still existed. On ultrasonography both testes were small as maximal diameter of 18 mm. He had no sperms on spermiogram. We started human chorionic gonadotropin alone and then we added menotropin to the therapy. After 12 months, he had still no sperms on spermiogram and no change of testicular sizes. We performed a chromosomal analysis to investigate other pathologies. A 46 XX genotype with deletions on regions SY84, SY86, SY127, SY134, SY254, and SY255 detected on the analysis. The result was considered as 46 XX male syndrome. Testosterone therapy was started instead of gonadotropin therapy.
Conclusion
The 46 XX male syndrome usually presents with hypergonadotrophic hypogonadism however in our case it presented with hypogonadotrophic hypogonadism due to pituitary mass.

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P701

Gonadal and sexual function in young/middle aged human immunodeficiency virus (HIV)-infected men

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Background
HIV-infection is associated to an increased prevalence of age-related comorbidities, such as erectile dysfunction (ED) and testosterone (T)-deficiency.
Aim
Definition of ED and T-deficiency in HIV-infected men using validated sexual questionnaires and the gold standard assay for T measurement: isotopic dilution–liquid chromatography–tandem mass spectrometry (ID–LC–MS/MS)
Methodology
Prospective, cross-sectional, observational study on 68 HIV-infected men (mean age = 44years) with ongoing highly active antiretroviral therapy (HAART). International index of erectile function (IIEF)-15 questionnaire was used to assess ED, considered for score <25 at erectile domain. Sexual function was studied also by structured interview on erectile dysfunction (SIEDY) questionnaire. ID–LC–MS/MS was used for hormonal assays. Serum total $T<300$ ng/dl was suggestive for T-deficiency.
Results
IIEF-15 erectile domain is impaired in 60.3% of patients, with a 13.2% of severe form. 11% of subjects declared the use of PDE5-inhibitors. SIEDY organic scale scores were significantly impaired in patients with hypertension ($P=0.013$) and hepatitis C virus (HCV) infection ($P=0.007$); psychogenetic scale was impaired only in HCV-infected men ($P=0.008$). T-deficiency is found in 10% of subjects with a longer time of HIV-infection and HAART. Comparing patients with or without T-deficiency IIEF-15 and SIEDY scores are similar in both groups.
Conclusions
The percentage of ED and T-deficiency is higher and occurs earlier in HIV-infected men than healthy subjects, supporting the hypothesis of premature aging in HIV-infection. However, serum T levels seem to be not correlated with IIEF-15 and SIEDY scores, suggesting that ED should not be directly related to the decline of serum T levels. Thus, HIV-infection itself, age-related comorbidities and psycho-emotional status seem to be the strongest risk factors in the development of ED. Furthermore, neither of validated questionnaires seem to be sufficiently trustworthy in the study of sexual function in HIV-infected men, but SIEDY could be more reliable than IIEF-15 when more comorbidities are present.

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P702

Effect of 17β-estradiol on germ cell apoptosis by modulating the expression of SCF/c-kit, FasL/FasR and regucalcin

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In the last years estrogens have emerged as important regulators in male reproductive function. Spermatogenesis depends on the tight control of germ cell apoptosis and several studies indicated estrogens as playing a role in this process. The stem cell factor (SCF), a membrane-bound cytokine, and its receptor (c-kit), and the Fas ligand (FasL)/Fas receptor (FasR) system are powerful mechanisms controlling germ cell proliferation and apoptosis through the direct membrane communication between germ cell and Sertoli cells (SCs). Also, regucalcin (RGN) a calcium-binding protein related with apoptosis may play a role in the control of germ cell death. Although estrogens are able to regulate the expression of SCF, c-kit, FasL, FasR and RGN in several cell types, its effect on the testicular expression of the aforementioned factors is unknown. Ex vivo cultures of rat seminiferous tubules (SeT) and primary SCs cultures were exposed to physiological (0.1 nM) or supraphysiological (100 nM) doses of 17β-estradiol (E_2) for 24 or 48 h. Also, selective agonists (100 nM) for classical and membrane-associated estrogen receptor (ER) subtypes were used. 100 nM E_2 induced a decrease in c-kit expression while increasing FasR, FasL and RGN levels. E_2 modulation of SCF/c-kit, FasL/FasR and RGN expression underpinned diminished proliferation and augmented apoptosis of germ cells, as indicated by Ki67 fluorescent immunohistochemistry, caspase-3 activity and Bax/Bcl-2 (proapoptotic/antiapoptotic) proteins ratio. Our results demonstrated that a supraphysiological dose of E_2 induces germ cell apoptosis by disrupting the survival/death communication between SCs and germ cells due to unbalanced expression of SCF/c-kit and FasL/FasR. Moreover, the use of ER selective agonists allowed suggesting GPER/GPR30 as the main receptor mediating estrogen-induction of apoptosis. Ultimately, these findings helped to clarify the mechanisms underlying male infertility associated with hyperestrogenism.

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P703

Evaluation of adipocytokine levels and vascular reactivity in hypogonadotropic hypogonadal males

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Introduction
Hypogonadism have major affect on urogenital system also have several affect on other systems like cardiovascular and skeletal systems. There are very few study conducted on markers of atherosclerosis such as flow mediated dilatation (%FMD), carotis intima-media thickness(CIMT) and adipocytokine levels in idiopatic hypogonadotropic hypogonadal(IHH) males. The aim of this study was to evaluate this atherosclerotic risk factors in adult IHH male.
Material and method
Study population consisted of 11 treatment naive IHH patients and 15 age-matched healthy male controls). A fasting blood sample was obtained for adrenal androgens, leptin, adiponectin and rezistin. The endothelial function was evaluated according to the flow-mediated vasodilation of the brachial artery (%FMD) and carotis intima-media thickness (CIMT) by high resolution B-mode ultrasound.
Results
Clinical features of the subjects participating in the study are reported in Table 1. No significant differences in age, BMI, systolic and diastolic blood pressure were recorded between two group. Leptin level was significantly higher in group 1, whereas adiponectin and rezistin level were same between two groups.
There was a negative correlatin between total testosteron and carotis intima-media thickness ($r=-0.656$, $P=0.008$), and a negative correlation between total testosteron and leptin level ($r=-0.794$, $P<0.001$). No correlation was found between leptin and CIMT ($P=0.184$).

Conclusion
Hypogonadal men had higher levels of leptin suggest leptin rezistance. Also had higher CIMT measurement. %FMD measurement were worser in IHH males bu it wasn't significantly different.

Table 1 Characteristics of hypogonadal (group 1, $n=11$) and eugonadal men (group 2, $n=15$)

	Group 1	Group 2	P
Age (years)	34.9±8.57	29.57±11.84	0.21
BMI (kg/m^2)	23.6	22.8	0.26
Total testosterone (nmol/l)	0.34 (0.18–1.89)	5 (4–5.2)	**<0.001**
Adiponectin (ng/ml)	4.41 (3.78–6.03)	5.25 (2.40–5.50)	0.81
Leptin (ng/ml)	14.92±9.33	4.36±1.71	**0.01**
Rezistin (pg/ml)	4633±2062.77	4058.29±1962.5	0.56
CIMT (mm)	0.80 (0.75–0.90)	0.55 (0.50–0.68)	**0.02**
%FMD	3.5 ((−0.40) −0.09)	−22.4 ((−0.37) −0.14))	0.12

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P704

Current smoking is associated with lower ejaculate and seminal vesicles volume but higher testosterone levels compared to no-smoking in males of infertile couples

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Introduction
Smoking habit has always been considered to exert a detrimental effect on male reproductive health. However, several studies do not clearly demonstrate a negative effect of smoke on semen parameters. In addition, the effect of smoke on male genital tract has been poorly studied by ultrasound (US). We evaluated the correlations of smoking with seminal and US characteristics in males of infertile couples. Methods. A consecutive series of 426 men was systematically evaluated. All patients underwent physical, biochemical, seminal evaluation (including seminal interleukin 8, sIL-8) and scrotal/transrectal US before and after ejaculation, Results. Among 426 men, 394 (36.0±8.0 years) without genetic abnormalities were studied. 229 were never-smokers (NS), 56 past-smokers (PS), 109 current-smokers (CS). PS were older compared to NS and CS. CS showed a significantly higher prevalence of alcohol and substance abuse, lower frequency of physical activity compared to NS or PS. CS showed higher testosterone (T) and lower FSH levels compared to NS or PS. CS had significantly lower semen volume, higher normal sperm morphology and higher sIL-8 levels compared to NS. At CDUS, CS and PS showed a lower seminal vesicles (SV) volume before and after ejaculation compared to NS. CS showed a higher prevalence of dilated ejaculatory ducts compared to NS. A further statistical analysis tested the previous significant associations by comparing CS ($n=109$) and no-smokers ($n=285$) adjusting for age, alcohol and substance abuse, physical activity, TT, BMI. After adjusting for confounders, CS showed higher risk for higher T levels (AdjOR: 1.06 [1.01–1.15], $P=0.01$), lower FSH (AdjOR: 0.41 (0.16–1.00), $P=0.05$), lower semen volume (AdjOR: 0.82 (0.68–0.98), $P<0.05$) and SV volume before and after ejaculation (AdjOR: 0.35 (0.14–0.89), $P<0.05$ and AdjOR: 0.31 (0.13–0.73), $P<0.01$ respectively) and higher risk for dilated ejaculatory ducts (AdjOR: 3.01 (1.26–7.19), $P<0.02$). Associations with normal sperm morphology and sIL-8 levels were not confirmed.
Conclusions
In males of infertile couples CS is associated with higher T levels, lower semen and SV volume and ejaculatory ducts dilation. CS may lead to lower semen volume by modulating SV volume, despite higher T levels compared to no-smokers, or promoting distal subobstruction.

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P705

Relationship among nutritional patterns, metabolic parameters and reproductive hormones In healthy young men

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Introduction
Even though the importance of nutrition in diabetes development is well known, little has been done to explore whether nutrition affects reproductive health and escalates the risk for further consequences of deterioration of metabolic parameters in young men.
The goal of our study was to evaluate a possible relationship between eating patterns, metabolic parameters and androgenisation levels in healthy young men.
Methods
A total of 199 men aged 18-26 participated in this sub-study. Anthropometric measurement included height, weight, hip circumference, waist circumference, and calculation of body mass index. Investigation of reproductive function consisted of clinical evaluation, including orchidometry and measurement of serum testosterone, sex hormone binding globulin (SHBG), estradiol and inhibin B levels. Body composition analysis was performed by bioelectrical impedance analysis. Nutrition questions included usage of milk and dairy products, eggs, different types of meat and fish, pulses, fruit and vegetables.
Results
A weak inverse correlation between beer consumption and SHBG has been observed ($r=-0.180$, $P=0.013$). Amount of wine consumed was related to estradiol levels ($r=0.211$, $P=0.007$). SHBG levels had inverse correlation with fat mass ($r=-0.258$, $P<0.001$), hip circumference ($r=-0.249$, $P=0.001$) and waist circumference ($r=-0.200$, $P=0.008$). Comparison of distributions among groups showed that milk non-users had lower testosterone ($P=0.032$) and estradiol ($P=0.033$) levels and higher waist circumference ($P=0.047$). More frequent usage of beef or veal was borderline associated with higher waist circumference ($P=0.043$).
Conclusions
Our data demonstrate that nutrition can be related to reproductive health and metabolic parameters in healthy young men. Consumption of milk is related to higher sex hormone levels. Beer consumption inversely correlated with SHBG levels, while wine consumption showed positive correlation with estradiol concentration.

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P706

Relationship of testis size and LH levels with incidence of major adverse cardiovascular events in older men with sexual dysfunction

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Introduction
Measurement of testis volume (TV) is a reliable clinical procedure that predicts reproductive fitness. However, the role of TV in overall and cardiovascular (CV) fitness has never been studied.
Aim
The study aims to analyze the clinical correlates of TV in patients with sexual dysfunction (SD) and to verify the value of this parameter and its determinants (i.e., luteinizing hormone (LH) levels) in predicting major adverse CV events (MACE).
Methods
A consecutive series of 2809 subjects without testiculopathy (age 51.2±13.1) consulting for SD was retrospectively studied. A subset of this sample ($n=1.395$) was enrolled in a longitudinal study.
Main outcome measures
Several clinical and biochemical parameters were investigated.
Results
After adjusting for confounders, TV was negatively associated with both LH (Adj. $r=-0.234$; $P<0.0001$) and follicle-stimulating hormone (Adj. $r=-0.326$; $P<0.0001$). In addition, overweight/obesity, smoking, and alcohol abuse increased as a function of TV (hazard ratio (HR)=1.041 (1.021–1.061), $P<0.0001$; 1.024 (1.005–1.044), $P=0.012$; 1.063 (1.015–1.112), $P=0.009$ respectively). Furthermore, mean blood pressure was positively related to increased TV (Adj. $r=0.157$; $P<0.0001$). The effect of these lifestyle factors on TV were only partially related to changes in gonadotropin levels. In the longitudinal analysis, after adjusting for confounders, TV was associated with a higher incidence of MACE (HR =1.066 (1.013–1.122); $P=0.014$), and the stepwise introduction in the Cox model of lifestyle factors, mean blood pressure and body mass index progressively smoothed out the association, which was no longer statistically significant in the fully adjusted model. Conversely, the association of higher LH levels with increased incidence of MACE was not attenuated by the progressive introduction of the aforementioned confounders in the model.
Conclusions
Our data show that in SD subjects, TV and LH are associated with an adverse CV risk profile that mediate the higher TV-associated incidence of MACE. High LH levels are an independent marker of CV risk. Further studies are needed for clarifying determinants and mechanisms of testis enlargement that, beyond gonadotropins, could mediate the increased incidence of MACE.

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P707

Lack of sexual privacy affects psychological and marital domains of male sexual dysfunction

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Introduction
Sexual dysfunctions (SD) are dictated by predisposing, precipitating, maintaining, and contextual factors, the latter of which can help sexual problems to emerge. Even if the lack of sexual privacy is one of the most common contextual issues, it has not been extensively studied.
Aim
Investigation of sexual privacy in a large sample of men consulting for SD.
Methods
A consecutive series of 3736 men, attending the Outpatient Clinic for SD for the first time, was retrospectively studied. Privacy during sexual intercourse was investigated with the following question 'During the last 3 months, have you had enough privacy during your sexual activity?', and rated 0 = yes, 1 = sometimes, 2 = rarely, 3 = never.
Main outcome measures
Several clinical, biochemical and psychological (Middlesex Hospital Questionnaire, MHQ) parameters were studied.
Results
Among the 3736 patients studied, 83.9% reported enough privacy during sexual intercourse, while 8.6, 5.7 and 1.7% declared a decrease of sexual privacy of increasing severity. Lack of sexual privacy was associated with ejaculatory dysfunctions and with the inability to maintain an erection during intercourse. Subjects reporting lack of sexual privacy had a higher risk of relational and intrapsychic impairments, as well as psychopathology at MHQ questionnaire, even after adjusting for confounders. Fatherhood was associated with sexual privacy issues only in the lowest quartiles. In subjects without children, the absence of cohabitation with the partner was associated with an increasing risk of not having enough privacy (HR = 1.837 (1.269–2.659), $P = 0.001$), data confirmed, after stratification for age, only in the youngest subjects (I quartile HR = 2.159 (1.211–3.848), $P = 0.009$).
Conclusions
This study indicates that sexual privacy is often a poorly investigated item, which is important to evaluate in male SD.

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P708

Regulation of pro-inflammatory cytokines (TNF-α and IL-6) secretion by LPS in immature rat peritubular cells

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The regulation of TNF-α and IL-6 secretion in LPS-stimulated Peritubular cells was investigated in vitro. Immature rat Peritubular cells were incubated with LPS (10 μg/ml) over 24 h culture. TNF-α and IL-6 were measured in the culture medium by ELISA at 24 h, TNF-α and IL-6 genes by real-time RT-PCR, and activation of NF-κB, MAPKs, and AP-1 signal transduction pathways by western blotting. LPS stimulated the mRNA expression of IL-6 and much more the expression of TNF-α (148-fold). In the presence of trichostatin-A (histone deaceytylase inhibitor), the mRNA expression of IL-6 but not TNF-α was potentiated, even when no detectable expression was observed in the TSA-alone treated cells. The degradation of IκBα was noticed at 30 min and then regains stable expressions afterwards. This corresponded with increased expressions of p-p38, NF-κB (p65) and p-JNK at the 30 min culture period. LPS also stimulated the secretion of IL-6, and there was no synergistic effect by TSA on IL-6 production. In contrast to IL-6, no detection of TNF-α was noticed in PTCs after LPS stimulation. These results suggest that the IκBα, MAPKs, and AP-1 signalling cascades are active in PTCs, and therefore, the immunosuppressive capacity of PTCs is compromised during LPS-induced testicular inflammation resulting to the increased secretion of IL-6.

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Neuroendocrinology

P709

Identification of the kisspeptin cells of the arcuate nucleus as 'pulse generators' for gonadotropin releasing hormone.

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Evidence from studies in goats[1], sheep[2] and mice[3] suggests that the kisspeptin cells of the arcuate nucleus generate the signal that causes the pulsatile secretion of GnRH. This effect may be due to action of kisspeptin on GnRH terminals in the median eminence[3,4]. We conducted studies on sheep to test the hypothesis that kisspeptin cells of the arcuate nucleus (ARC) and/or the glutamate cells of the hypothalamus pulses of GnRH secretion.
Blood samples were taken each 10 min for 3 h from 18 ewes in the luteal phase of the estrous cycle. The animals were euthanased and the brains perfused with 4% paraformaldehyde. LH assays showed that 3 animals had a pulse of luteinising hormone (LH) within 30 min of brain collection. In these (pulse) and 3 other animals (non-pulse) we determined the number of GnRH, kisspeptin and glutamate cells in the hypothalamus that co-stained for c-Fos. Sections were cut through the ARC and the preoptic area (POA) and the peptides were visualised in cells by immunohistochemistry. The sections were then co-stained for c-Fos as an indicator of neuronal activation. Pulse generation was associated with a significant ($P < 0.002$) increase in the mean (±S.E.M.) percentage of ARC kisspeptin cells with c-Fos staining (pulse −74.9±2.5% *vs* no pulse −, 34.4±6.1%). In the ARC, more ($P < 0.01$) glutamate cells were c-Fos labelled (27.6±4.4) in pulse animals than in non-pulse animals (5.8±0.6). There was no difference in the number of kisspeptin, glutamate or GnRH cells co-staining for c-Fos in the POA.
These data suggest that kisspeptin cells of the ARC generate GnRH pulses, but glutamate cells may also be involved.
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P710

Meal-induced plasma ghrelin suppression in different phases of anorexia nervosa

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Introduction
The ghrelin suppressive effect of food is well established in normal subjects, whereas the effectiveness of meals in decreasing plasma ghrelin in patients with anorexia nervosa (AN) is still debated. Based on the above, we elected to study the ghrelin dynamics after food or placebo in a group of anorectic girls at the moment of diagnosis and after weight recuperation.
Study design
Nine anorectic women (age 14–32 years) were studied. Both in the acute phase of the disease and after 2–6 months of nutritional rehabilitation, in each patient, on two separate occasions and in random order, plasma total ghrelin was measured along the two hours following the ingestion of a 585 kcal meal or fiber as placebo.
Results
Nutritional rehabilitation induced a significant increase in mean BMI (from 15.2±0.35 to 16.9±0.34 kg/m^2, $P < 0.01$). Both in the acute and recovery phases of AN, fiber consumption failed to significantly modify ghrelin levels (from 1433.5±393.00 to 1240.3±273.24 pg/ml, NS, and from 1090.0±279.86 to 1084.6±252.89 pg/ml, NS respectively). In both phases of the disease, food significantly reduced circulating ghrelin (from 1294.1±270.51 to 929.2±203.55 pg/ml, $P < 0.01$, and from 1294.3±320.66 to 927.8±252.07 pg/ml, $P < 0.01$ respectively), and this decrease was of the same entity in the acute (to 74.3±5.32% of baseline) and the recovery (to 72.0±3.52% of baseline) phases. At diagnosis the mean absolute ghrelin decrease induced by meal was significantly greater than that following fiber (364.8±99.70 *vs* 193.1±125.09 pg/ml, $P < 0.01$), and the same held true after weight gain (366.4±82.84 *vs* 5.3±70.26 pg/ml, $P < 0.01$).
Comment
The ghrelin suppressive effect of food appears to be maintained in the acute phase of AN and no changes can be seen after significant weight gain during nutritional rehabilitation.

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P711

Acromegaly and pregnancy: A descriptive case series

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To describe the course of acromegaly in a group of seven women, before, during, and after pregnancy.
Methods
Descriptive case series of acromegalic pregnant women attending a reference health center in Cali, Colombia.
Results
Mean age at conception was 29 ± 10 years, starting prenatal care at 10 ± 3 weeks of gestation. 6 of 7 patients had a macroadenoma as evidenced by neuroimaging (MRI). 43% (three cases) had GH and prolactin co-secretion. The mean time from the moment of diagnosis until conception was 67 ± 32 months. Hypertension was documented in a single patient and none had diabetes mellitus. Before conception, the co-secretion of GH/IGF1 had remained under control. One patient showed normal levels of IGF1 = 319 ng/ml (109–483 ng/ml) with this prevailing tendency throughout pregnancy. All patients had received surgical treatment before pregnancy, with an average interval between surgery and conception of 3.3 ± 2 years. Seven patients had undergone medical treatment prior to conception: octreotide (three cases), cabergoline (two cases), lanreotide and bromocriptine (one case each respectively). Two of the seven patients (28.6%) developed gestational diabetes, while three of seven patients (43%) developed pregnancy hypertension. All women breast-fed. During pregnancy, four women (57%) received medical treatment: lanreotide (two cases), octreotide (one case), and cabergoline (one case). 86% had cesarean delivery ($n = 6$). GH/IGF1 levels in all patients remained elevated during the first month postpartum. Tumour size increased and decreased in two and three cases respectively, remaining unchanged in one case. Newborns had a mean gestational age of 38 ± 1.2 weeks, average length and weight of 50.4 ± 2.6 cm and 3,100 ± 537 g respectively. A single case of low birth weight was documented in a newborn infant of 2,123 g. No cases of macrosomia or other comorbidities were reported.
Discussion
Although fertility is commonly impaired in acromegaly, spontaneous conceptions can occur. The patients reported here were treated with somatostatin analogs during pregnancy. Gestational diabetes and pregnancy hypertension were reported.

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P712

Papillary thyroid carcinoma associated with silent paraganglioma: An atypical MEN syndrome?

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Case
A 51-year-old-woman was referred to endocrinology outpatient clinic due to a thyroid nodule 9 mm in diameter. Fine needle aspiration (FNA) biopsy revealed papillary thyroid carcinoma and she was directed to surgery. The surgeon decided to perform subtotal thyroidectomy due to the small nodule size. Pathologic examination showed the histology to be consistent with tall cell carcinoma. Complementary total thyroidectomy was proposed to the patient but she did not accept the second operation. During close follow-up for two years, thyroglobulin levels were high about 4 mg/dl and there were reactive cervical lymphadenopathies which were 2.5 cm in diameter. PET/CT was performed to be sure about any metastasis. Surprisingly, a 7 × 5 cm hypodense lesion, with a high FDG uptake was detected in the mid-upper abdominal region and the mass was suspected to be lymphoma first. In the abdominal CT scan, 6.7 × 5.9 × 6.6 cm retroperitoneal mass was located at the aortacaval region (Fig. 1). The patient was consultated with the hematology department and they recommended FNA biopsy to be performed from the mass. During the biopsy procedure, no clinical symptoms were evident and the pathologic diagnosis was reported to be a paraganglioma.24 h urine fractioned metanephrine levels were markedly elevated and I^{131}-MIBG showed significant uptake by the mass. Chromogranin-A level was very high whereas PTH and calcitonin were in normal ranges. Surgery was performed for the abdominal paraganglioma after the patient was prepared for the operation with alpha-blocker agents although she did not have a hypertensive attack or any clinical finding before. The excised mass was 10 cm in diameter and the pathology was reported to be grade I neuroendocrine tumor without Ki67 proliferation.
Three months after the operation, 24 h urine fractioned metanephrines and MIBG scan were normal.
Consciously, thyroid protection with iodine was not carried out during MIBG procedures so thyroid gland shrank in size. Radioactive iodine ablation therapy was performed for thyroid papillary carcinoma successfully. Thyroglobulin level decreased after ablation.
The patient remembered that her mother had a mass in her neck which could have been paraganglioma. SDHD/SDHB and RET mutation analyses were planned and we are still waiting for the results.
Discussion
Papillary thyroid carcinoma associated with pheochromocytoma had been reported previously both sporadically and with MEN syndromes but rarely with a paraganglioma. SDHD or SDHB mutation (for paraganglioma) and RET proto-oncogene (for MEN) analysis are important for diagnosis of genetic basis of the diseases. The relationship between these two lesions could not still be determined in our case. Recently, a case with papillary thyroid carcinoma associated with paraganglioma and Dandy-Walker Malformation was reported whose SDHD mutation positive[1]. The authors have noted that SDHx mutations can cause familial paraganglioma syndromes. In our case if mutation analysis reveals positive results, these combinations could be explained as an atypical MEN syndrome or a subtype of MEN syndrome.

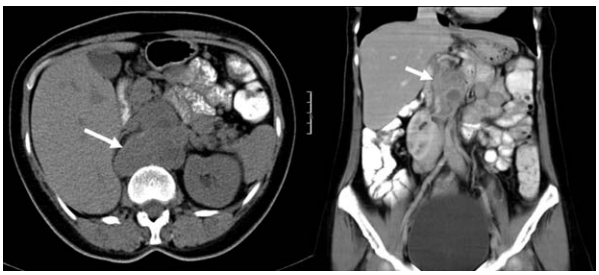

Figure 1 The arrows show retroperitoneal aortacaval mass in abdominal CT (transverse and coronal images)

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P713

Copeptin for the differential diagnosis and therapy management of hyponatremia in hospitalized patients – 'The Co-MED-Study'

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Background
Hyponatremia is common in hospitalized patients and its differential diagnosis and management challenging. An important mechanism is suppressed or adequately or inadequately secreted plasma arginine vasopressin (AVP). Therefore, plasma vasopressin levels may help in the differential diagnosis and in therapy management. Copeptin is secreted in an equimolar ratio to AVP and is more reliable to measure.
Methods
In this prospective observational multicentre study 298 consecutive patients admitted to the emergency department with severe hypoosmolar hyponatremia (Na < 125 mmol/l) were included. After a standardized diagnostic evaluation patients were treated according to a diagnostic algorithm. Copeptin levels were compared between different aetiologies of hyponatremia and for prediction of therapeutic management.
Results
We found 24 patients (8%) with primary polydipsia, 72 patients (24%) had diuretic induced hyponatremia, 106 (36%) patients SIAD, 4 (1%) patients cortisol deficiency, 33 patients (11%) hypervolemic hyponatremia and 59 patients (20%) hypovolemic hyponatremia. Overall Copeptin levels discriminated between various aetiologies of severe hyponatremia ($P < 0.0001$). Copeptin levels were higher in patients requiring saline infusion ($n = 139$) as compared to patients

requiring fluid restriction ($n=159$) (21.40 (8.00–65.60 pmol/L) vs 12.16 (IQR 5.13–28.15) pmol/l, $P=0.0003$). A copeptin level >56.8 pmol/l allowed a diagnosis of hypovolemic or diuretic induced hypovolemia requiring saline infusion with a specificity of 86%. Conversely, a copeptin level <4.4 pmol/l identified patients with need of fluid restriction with a specificity of 91%. In multivariate analysis copeptin, fractional uric acid excretion (FE uric acid) and volume status were independently associated with therapy management. The combination of these three factors showed a high prognostic accuracy for therapy management (AUC: 0.77 (95% 0.71–0.83).

Conclusion

Copeptin levels identify a subset of patients with a need of saline infusion or fluid restriction and may be a helpful new tool for therapeutic management. The best prediction of therapeutic management is achieved when combining copeptin, volume status and FEuric acid.

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P714

Clinical symptoms and characteristics of hospitalized patients with severe hyponatremia

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Background

Hyponatremia is the most common electrolyte disturbance in hospitalized patients and associated with a substantial morbidity and mortality. Symptoms of severe hyponatremia vary among patients between nonspecific symptoms such as nausea or malaise or acute life threatening brain oedema. Prospective studies to assess symptoms and mortality in patients with severe hyponatremia are lacking.

Methods

In this prospective multicentre observational study 298 patients admitted to the emergency department with severe hypoosmolar hyponatremia (Na< 125 mmol/l) were included. All symptoms, complete medical history including current medication, therapy management and in-hospital mortality were recorded.

Results

Median age of all patients ($n=298$) was 71 (IQR 60–80), 195 (65%) were female and serum sodium values on admission were 120 (IQR 116–123) mmol/l. 130 patients (44%) complained about nausea and 91 patients (30%) had a history of vomiting. Moreover 205 (69%) patients indicated generalized weakness and 175 (59%) fatigue. 92 patients (31%) had disturbed gait, 47 patients (16%) had a history of recurrent falls and 60 patients (20%) had an acute fall leading to hospitalization. Fractures were reported in 11 patients (4%). More severe symptoms such as seizures or focal neurological deficits were identified in 16 patients (5%) and 32 patients (11%) respectively. The most common comorbidity was hypertension (199 patients, 67%), 44 patients (15%) suffered from congestive heart failure, 64 patients (21%) had chronic renal failure, 82 patients (28%) had pulmonary diseases and 113 patients (38%) had a central nervous system disease. During hospitalisation 12 patients (4%) died and 103 patients (35%) needed treatment at the intensive care unit.

Conclusion

Severe hyponatremia is accompanied by a wide spectrum of symptoms. Most patients suffered from moderate symptoms reflecting rather chronic hyponatremia with brain cell adaptation. Patients presenting with severe hyponatremia had several comorbidities.

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P715

Clinical manifestations of neurofibromatosis type 1

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Introduction

Neurofibromatosis type 1 (NF1; von Recklinghausen's disease) is an autosomal disorder with the prevalence 1 in 3,000 births. It is caused by mutation of the tumour-suppressor gene encoding neurofibromin. NF1 may affect various organs and patients are at increased risk of developing many neoplasms.

Material and methods

We analysed seven cases of patients with NF1 (four females and three males) aged 19–52 who were treated at Endocrinology Department between 2003 and 2013 to describe clinical manifestations. In studied subjects, the diagnosis was made in childhood (four patients) or in adolescence (three cases), based on clinical symptoms and genetic tests as well.

Results

Five patients had a positive family history of NF1, two cases represented spontaneous mutation. All of analysed subjects presented café-au-lait spots and neurofibromas on the body. Neurological disorders such as: epilepsy (two patients) and Arnold–Chiari malformation (one man) have been observed. Benign brain neoplasms developed in two persons. Optic gliomas appeared in two cases: one man had a surgery and received radiotherapy due to optic chiasma astrocytoma, one woman was operated because of bilateral optic gliomas. Tumours were also found in other organs: leiomyomas in the uterus (two woman) and pheochromocytoma, nodule of the lung, adenoma in the pituitary gland and parathyroid adenoma with primary hyperparathyroidism – in one patient each. Four patients suffered from cognitive impairment. Moreover, we observed skeletal manifestations of NF1 such as scoliosis (one man) and short stature (six patients). Most of analysed subjects presented thyroid disorders, including hypothyroidism due to Hashimoto's disease (four patients) and toxic nodular goiter (one woman). Other clinical symptoms such as: vitiligo, alopecia areata and coarctation of the aorta have also been found.

Conclusion

Variety of clinical symptoms causes that NF1 still remains diagnostic and management challenge for many physicians. Therefore, multidisciplinary approach is needed to optimize patients' treatment.

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P716

Long-term remission and recurrence rates after transsphenoidal surgery for cushing's disease

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Objective

Transsphenoidal surgery (TSS) presents the treatment of choice for Cushing's disease (CD), 95% microadenomas. Remission and recurrence rates vary dependent on tumor size, extension, adenoma visibility on magnetic resonance imaging, and neurosurgical expertise. Remission rates in the postoperative vary between 55 and 85%, with a recurrence of up to 25%. The aim of this study was to describe the rate of remission and recurrence of CD in our midst after TSS, and compare it with that described in the literature.

Patients and methods

We conducted a retrospective analysis of patients who underwent as TSS for CD between 1994 and 2013. Variables analyzed: age, sex, time to diagnosis, tumor size, serum cortisol, urinary-free cortisol (UFC), remission, persistence and recurrence of CD. Remission was defined as normalization of serum cortisol and UFC levels, persistence as no normalization of serum cortisol and UFC levels after TSS and recurrence as presence of elevated serum cortisol and UFC levels after having achieved remission.

Results

Thirty-eight patients with CD treated with TSS. 42.76±14 years old. Women: 83.7%. Time to diagnosis: 30.39±29.67 months. Macroadenomas 28.9% ($P=0.01$), tumor size 8.68±75 mm. Remission 52.6% ($P=0.21$), persistence 13.2% and recurrence 34.2% ($P=0.77$). Adrenal insufficiency: 13.2%. Time from surgery to recurrence: 49.23±50.8 months. Treatment of recurrent: 42.9% TSS, 50% radiotherapy and 2.6% medical treatment. Second recurrence: 8%. Remission of CD at the end of the follow-up: 72.2% ($P=0.26$). Death: 2.8%.

Conclusions

CD is more common in women in the fourth decade of life. Remission and recurrence of CD is similar to that described in the literature. Percentage of macroadenoma is higher than reported in other series.

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P717

A rare incident of gastric mucinous adenocarcinoma in an acromegalic patient

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Acromegaly is frequently associated with tumor development of various organs, mostly with cancer of colon and thyroid gland while the development of gastric cancer is a very rare condition.
We observed a 33-years-old woman with mild clinical signs of acromegaly. The diagnosis was confirmed by laboratory tests (increased levels of IGF1 and growth hormone – 573 ng/ml and 9.8 ng/ml respectively) and MRI (supra-infra-latero-cellary pituitary adenoma, 9×20×18 mm) (September 2006). The patient received injections of Sandostatin LAR with maximum dose 40 mg per 28 days and dopamine agonists due to low sensitivity to the drug.
During next 2 years the patient regularly underwent a complex examination. According to diagnostic tests no hormonal remission of acromegaly was reached, but the patient refused from repeatedly recommended surgery. According to next gastroendoscopy (20 April 2007) a superficial antral gastritis associated with *H. Pylori* was diagnosed and necessary therapy was conducted.
At the end of August 2008 the patient noticed the increase of her abdomen size and discomfort in the epigastric area. According to the ultrasound there were the pelvic ascites and signs of bilateral ovarian tumors. The diagnosis of bilateral ovarian cancer was suspected. While preparation to the surgical treatment of ovarian cancer, the gastroscopy was done: the infiltrating ulcer of gastric body and pyloric channel was revealed. According to histological results the mucinous carcinoma of the stomach was found. Thus, the tumors in the ovaries were metastases of gastric cancer. Patient refused from surgical treatment of cancer and died in two and a half months from approval of diagnosis. This case demonstrates the aggressiveness of cancer in patients with acromegaly and it needs further studies of this problem

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P718

Bilateral ovariectomy and neurodegeneration

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Bilateral ovariectomy (OVX) in female rats cause neurodegeneration in the nervous system of rodents and imitates systemic disorders in postmenopausal women's organism. Synaptic modulation by estrogen is essential to understand the molecular mechanisms of estrogen replacement therapy. The aim of present work was to determine the action of Sinestrol on rats' hippocampal synaptic transmission, plasticity and cell survival in condition of bilateral OVX. Electrophysiological and morphohistochemical (by revealing Ca^{2+}-dependent acid phosphatase) studies by extracellular recording of hippocampal single-neuronal spike activity under high-frequency stimulation (HFS) of entorhinal cortex (EC) were performed on: 1) intact Albino rats, 2) after 8 week of OVX (placebo-control), 3) after 8 week of OVX (after 3 weeks i.m. injection of Sinestrol- 0.1 ml 2%). Our data suggest that OVX reduces hippocampal synaptic activity and failures the balance of excitatory and inhibitory responses of norm. After 8 week following OVX in hippocampal neurons dominate effects of tetanic depression in combination with posttetanic potentiation (45%) in response to HFS EC and typical of presence of areactive neurons (21%). Sinestrol promote the reorganization of neuronal circuitries of cortex-hippocampus by modulation of anomalous synaptic activity, as well as the balance of areactive and reactive units. Morphohistochemical analysis of studies by revealing Ca^{2+}-dependent acid phosphatase testify that in whole Sinestrol enhances phosphorylation processes providing optimization of regeneration process following OVX.

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P719

Effects of pharmacological blockade of glucocorticoids on energy homeostasis control by liver and pancreas in rats without pineal gland

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In liver, melatonin (Mel) and glucocorticoids (GC) influence the systemic energy homeostasis. Animals without pineal gland present impairment in glycemic control, as in type-2 diabetes. In turn, Mel reduces the GC levels, particularly in nocturnal animals. We aimed to evaluate the influence of Mel, as well as GC receptor blockade by RU486 treatment on hepatic and pancreatic energy metabolism. Male Wistar rats were subjected to surgical removal of pineal and, 25 days after the surgery, treated with vehicle (PX) or RU486 (PX RU; 0.5 mg/100 g per 5 days). All the experiments were conducted at the end of the light phase of the light/dark cycle (ZT10). Animals were weighed and subjected to analysis of body composition by in vivo imaging system (FX PRO). Reduction of body weight (16%), muscle mass (41%) and adiposity (30%) was found in PX group, which was reversed by RU486 treatment. Circulating corticosterone were 30% higher in PX compared to control group (CTL, $P \leq 0.05$), despite the reduced glycemia (8%) and insulin levels (37%), both reversed by RU486 treatment. Additionally, PX increased in 28% the hepatic glycogen content, measured by digestion assay and histology (PAS). RT- PCR from liver tissue showed reduced mRNA to GCK (40%) in PX rats, compared to CTL ($P \leq 0.05$). PX RU showed increased mRNA to SREBP1c (10%), as well as decreased mRNA to PEPCK and G6Pase, compared to CTL ($P \leq 0.05$). The pancreatic islets were isolated from rats and incubated at four different glucose concentrations for measurement of insulin secreted (GSIS). Our results indicate increased insulin secretion in PX and PX RU in all concentrations analyzed. This finding corroborates overall results indicating that glucose intolerance in PX rats is characterized by hepatic insulin resistance and pancreatic insulin hyper secretion which can be a result of higher corticosterone levels.

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P720

Copeptin levels measured after pituitary surgery predict later development of diabetes insipidus

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Introduction
Postoperative diabetes insipidus (DI) remains a common complication after pituitary surgery. AVP measurement might contribute to a straightforward diagnosis, though, its measurement is cumbersome. Copeptin, the stable C-terminal glycopeptide of the AVP prohormone, is a reliable surrogate of AVP. We aimed to elucidate whether copeptin is a helpful marker in the diagnostic approach of postoperative DI.
Methods/design
Prospective observational study in three tertiary referral centres in Switzerland and Canada. Patients undergoing pituitary surgery were daily monitored for clinical items (i.e. balance of fluids) and routine laboratory parameters. Copeptin levels were measured pre- and daily postoperatively until discharge. We also recorded tumour specific features and intraoperative manipulation of the neurohypophysis.
Results
Of the 205 patients included (mean age 53 years, 55.6% female) 50 (24.4%) developed postoperative DI, 155 patients had an uneventful postoperative course or developed SIADH (5.4%). The median copeptin levels measured preoperatively were 3.6 pM (IQR 2.4, 5.7) and increased more than two-fold to 8.4 pM (IQR 3.9, 22.6) after surgery. Copeptin levels of patients developing DI did not increase during surgery-induced stress and were lower postoperatively compared to patients without DI (median (IQR) 2.9 pM (1.9, 7.9) vs 10.8 pM (5.2, 30.4), $P < 0.001$). This was most pronounced in a subset of 157 patients with early (< 12 h) postoperative copeptin measurement (median (IQR) 2.9 pM (1.8, 10.3)

vs 17.0 pM (7.6, 39.1), $P<0.001$).In patients with postoperative copeptin values <2.5 pM the positive predictive value for development of DI was 81% (specificity 97%). Conversely, if copeptin increased to levels >20 or >30 pM, negative predictive values and sensitivities were 93%/95% and 95%/98%.
Conclusion
Low postoperative copeptin levels despite surgery-induced stress indicate later DI. Copeptin may become a novel tool in the management of patients after pituitary surgery.

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P721

Multiple endocrine neoplasia presenting with a novel mutation on menin gene

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Introduction
Mutations on menin gene are associated with multiple endocrine neoplasia type 1.
Case report
Thirty-five year-old male patient was admitted to our hospital with history of recurrent syncope episodes for 5 years which were attributed to hypoglycemia. In physical examination, he had obesity and multiple papillamatous skin lesions on his abdominal region. He had no family history of similar symptoms. His laboratory eveluation was consistent with insulinoma. There were three pancreatic masses found on CT, two pancreatic masses found on Ga68 DOTANOC scintigraphy. After selective arterial calcium stimulation, there were increased insulin secretion found in the uncinate process and the tail of the pancreas.
In addition serum calcium and parathyroid hormone levels were elevated. Parathyroid lesions in the inferior part of the right and left thyroid gland were detected both with ultrasonography and MIBI scintigraphy. Pituitary hormone levels were at normal range. The skin lesions were diagnosed as fibroepithelial polips with excisional biopsy. He was diagnosed as multipl endocrine neoplasia type 1 including insulinoma, primary hyperparathyroidism and skin lesions.
Subtotal parathyroidectomy was performed which showed hyperplasia of parathyroid glands. Then, a distal subtotal pancreatectomy with enucleation of the mass located in the uncinate process was performed. Histopathology showed nine discrete insulinoma focuses. Genetic analyses showed a novel two base-paired deletion mutation as c.284 del CT heterozygote mutation on *MEN1* (menin) gene that can be associated with multiple endocrine neoplasia type 1. After 6 months, he is on insulin therapy without any hypoglycemic episodes.
Conclusion
Here we report a novel case of c.284 del CT heterozygote mutation on menin gene that can be associated with multiple endocrine neoplasia.

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P722

Long-term remission and recurrence rate in a cohort of Cushing's disease: The need for long-term follow-up

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Introduction
Transsphenoidal surgery (TSS) is the procedure of choice in Cushing disease (CD), with immediate post-operative remission rates ranging between 59 and 94% and recurrence rates between 3 and 46%, both depending upon the definition criteria and the duration of the follow-up. Our aim was to assess the rate of remission, recurrence and persistence of the disease after the first treatment and to identify predictors of remission in the CD population of our center during the last 40 years.
Methods
Retrospective cohort study of the patients diagnosed of CD and with complete follow-up in our center between 1974 and 2011. We analyzed 41 patients (35 women and 6 men) with a mean age at diagnosis of 34 ± 13 years and mean follow-up of 14 ± 10 years (1–37years).
Results
Thirty-five (85.4%) patients underwent transsphenoidal surgery as first treatment option. Histopathological evidence of a pituitary adenoma was registered in seventeen (48.5%) patients. Thirty-two (78%) patients achieved disease remission after the first treatment, 21 (65.6%) of them presented disease recurrence. Persistent disease was observed in 9 (22%) patients. Twelve (29.3%) subjects developed post-surgical adrenal insufficiency; seven of them (70%) achieved stable remission. Two parameters were found to be significant predictors of remission after the first treatment: age at CD diagnosis and the development of adrenal insufficiency (cortisol <3 ug/dl) in the immediate post-operative state. The overall rate of hypopituitarism observed in our serie was 53.7%, significantly higher when compared to other studies.
Conclusions
The recurrence rate in our serie is higher than in many others probably due to the long follow-up time. Early post-surgery adrenal insufficiency predicts remission rate. Hypopituitarism was also higher and strongly associated with radiotherapy. This leads us to the conclusion that CD needs a life-long strict follow-up.

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P723

Cinacalcet hydrochloride more efficiently controls serum calcium levels in mild-asymptomatic primary hyperparathyroidism without surgery criteria, as compared with surgical cases

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Context
Primary hyperparathyroidism (PHPT) is a common endocrine disease, characterized by the chronic elevation of serum calcium (Ca) levels induced by a long-standing increase of PTH concentrations. PHPT includes mild-asymptomatic and symptomatic forms. Cinacalcet is effective in lowering serum Ca levels in PHPT, but is indicated solely in mild-asymptomatic PHPT meeting surgery criteria. Management of non-surgical mild-asymptomatic PHPT is still a debated issue.
Objective
To compare biochemical efficacy of cinacalcet in controlling Ca levels in mild-asymptomatic PHPT patients fulfilling or not surgery criteria.
Design
This was a retrospective longitudinal cohort study.
Patients
Forty-three sporadic PHPT patients (mean age 62.5 ± 10.6 years) with mild-asymptomatic disease, treated with cinacalcet were included. Two categories were individualized: 23 patients with (category 1) and 20 patients without (category 2) surgery criteria. Median follow-up was 42 months.
Results
At the end of the initiation phase (3-months period with administration of 30 mg qd of cinacalcet), the proportion of patients achieving normocalcemia was significantly greater in the group without indication to surgery (category 2) compared to the group fulfilling criteria for parathyroidectomy (category 1) (90 vs 56.5%; $P<0.001$). During the length of the study, normalization of serum Ca levels was observed in all enrolled subjects. Median (minimum, maximum) daily dose of cinacalcet effective for obtaining and maintaining normocalcemia was 60 (30, 120) and 30 (30, 45) mg in categories 1 and 2 respectively. Mean time of Ca normalization was significantly lower in category 2 rather than category 1 (3.1 vs 4.2 months; $P<0.001$). Mean serum Ca levels were significantly lower in patients without surgery indication (category 2) rather than subjects fulfilling surgical criteria (category 1) at 6, 12, and 36 months.
Conclusions
Cinacalcet is more effective in controlling serum calcium levels in non-surgical cases of mild-asymptomatic PHPT. Cinacalcet treatment should be considered in mild-asymptomatic PHPT, independently from the presence of surgery criteria.

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P724

Treatment of SIADH in a patient with fatal familial insomnia (FFI) and hypersomnia

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Introduction
Fatal insomnia is a neurodegenerative spongiform prion disease. Presentation can be sporadic or hereditary (autonomal dominant). The latter, FFI, is caused by a mutation in the human prion protein gene on chromosome 20. Affected individuals present a disorderd sleep-wake cycle, dysautonomia and motor signs, with a predominance of lesions in the thalamus. SIADH has been described in two affected patients.
Case Study
A 70-year-old woman was referred to Endocrinology in July 2013 for the study of hyponatremia, following detection of a serum sodium level (SNa) of 124 mmol/l three weeks earlier, that did not respond to poorly-tolerated fluid restriction. The patient started with nocturnal insomnia in March 2013. In June she started presenting severe diurnal hypersomnia that interfered with her normal activites. Neurological diagnosis was: FFI (D-178-N mutation with methionine–methionine polymorhphism in codon 129) with hypersomnia (present in up to 50% of cases). She presented an altered gait, and mood swings. Previously diagnosed of depression, she had been on Trazadone and benzodiazepines for 2 years, without prior hyponatremia. Family history: one sister and three first-degree cousins had died with the diagnosis of FFI. Physical examination: euvolemia, bradypsychia, altered gait, and hyperreflexia. SNa: 129 mmol/l, urine sodium:135 mmol/l, plasma osmolality(Osm):269 mOsm/kg, urine osm:490 mOsm/kg. Normal renal, adrenal, hepatic, thyroid tests. Normal cervicothoracic CT, brain MR. Tolvaptan was initiated, attaining/maintaining eunatremia (SNa 137) with 60 mg/day. Median SNa pre-treatment:130.5 (126–132). On tolvaptan: 135.5(133 138) ($P=0.018$). Eunatremia was accompanied by resolution of patient's hypersomnia, bradypsychia, with mood improvement, and normal gait. The patient resumed intellectual and leisure activities, and an active social life, drinking freely.
Conclusions
Our patient, diagnosed with the Hypersomnia form of FFI, presented resolution of hypersomnia and other symptoms following treatment of her SIADH-induced hyponatremia with tolvaptan, permitting a normal lifestyle anew. We believe that all patients with FFI and hypersomnia should be screened for hyponatremia.

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P725

If there are differences in postoperative pituitary dysfunction in patients with micro and macroadenomas.

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Aim
To estimate pituitary disfunction development in patients with micro and macroadenonas before and after transnasal adenomectomy.
Methods
A total of 222 patients at the age from 17 to 71 with pituitary adenomas were operated from 2007 to 2013. According to size the pituitary adenomas were classified as microadenomas (diameter less than 10 mm) and macroadenomas (more than 10 mm). Dynamic observation and redetermination of all hormones were performed within 1, 3 and 12 months postoperatively.
Results
Before the surgery pituitary hormone deficiency had been found in 32.2% patients with pituitary macroadenomas: diabetes insipidus – 2%, secondary hypothyroidism – 9%, secondary adrenal insufficiency – 10%, hypogonadotropic hypogonadism – 13%. Their combination was found in 2% of cases. Among microadenomas preoperative hormone deficiency was not detected.
In 2.2% of patients postoperative recovery of pituitary function was observed (1 case of hypothyroidism, 1 – adrenal insufficiency, 2 – hypogonadism). Newly developed postoperative hypofunctions were recorded in 9% (3% of microadenomas, 19% of macroadenomas): diabetes insipidus – 9.9%, secondary hypothyroidism – 9%, secondary adrenal insufficiency – 2.2%, hypogonadotropic hypogonadism – 3.6%, cerebral salt-wasting syndrome – 0.45%. Combination of several postoperative hypofunctions was diagnosed in 3.5%, panhypopituitarism was diagnosed in 7%. There were no significant differences in types of postoperative pituitary dysfunction in patients with micro and macroadenomas. Postoperative hypopituitarism was diagnosed in the first 7 days after surgery in all cases. During the dynamic observation within 1, 3 and 12 months postoperatively new cases of hypopituitarism were not detected.
Conclusion
In patients with macroadenomas hypopituitarism develops more often, patients with microadenomas are also at risk. Data concerning pituitary functions over long term follow up in patients with adenomas is contradictory, so we recommend all patients after transnasal surgery undergo short and long term monitoring to exclude hypopituitarism.

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P726

Radiotherapy or surgical treatment, may affect response of cabergoline in the giant prolactinomas? Report of two cases

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Dopamine agonists are the treatment of choice for prolactinomas and surgery is warranted only when the response to medical therapy is poor, not tolerated, or in those with compromised vision or with extensive invasion. We describe the two cases of a giant prolactinoma treated with cabergoline alone and next to surgery and gamma-knife.
Case 1
A 30-year-old man admitted with headache and visual defect, cranial magnetic resonance imaging (MRI) revealed a invasive giant-adenoma with 50% cystic mass and dimensions of $47\times30\times27$ mm in size on the sellar area. Prolactin level was >1000 ng/ml with other tests showed no abnormality other than hypogonadism. Cabergoline was started with 1gram per week with twice dosing and was increased up to 3 g. After 3 months MRI revealed significant reduction in tumor size ($30\times22\times18$ mm) with subacute hemorrhagic changes. Prolactin level was down to 25 ng/ml at 3rd month and to 4 ng/ml at 6th month. Hypogonadism findings improved, and visual field showed marked improvement.
Case 2
Another man with 34 years was evaluated by a neurosurgeon at another institution due to headache and confusion. He has operated due to significant signs of compression with invasive giant-prolactinoma containing large cystic areas and $45\times33\times20$ mm in size detected with cranial MRI. Preoperative prolactin level was >1000 ng/ml. Cabergoline was started immediately postoperatively and gama-knife surgery was performed subsequently. In this case MRI findings at 3rd and 6th months were not showed improvement in tumor size and prolactin level was 250 ng/ml when admitted to us.
In the first case, cabergolin treatment has been effective for giant prolactinoma although containing cystic structures, in the second case it could not improvement in tumor size. Compared to the two cases, can be suggested that early surgical intervention or radiotherapy may have caused this ineffectiveness.

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P727

Hyperprolactinemia in women and men

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We analyzed data of 148 patients (125 female, 23 male) with hyperprolactinemia who had been investigated in our Department during 2008–2012: Nontumor hyperprolactinemia (NT, $n=46$, 31%), microadenomas (MI, $n=56$, 38%), MAcroadenomas (MA, $n=46$, 31%). Patients' age was 36 (24; 46), 37 (26; 44) and 49 (33; 60) years respectively. Men were younger than women ($P=0.002$).

Portion of men was higher in MA than in NT and MI: 19% *vs* 10 and 11%. Median prolactin levels were in NT 1547 (1124; 2185), MI 1490 (1050; 2280), and MA 3800 (1790; 18840) mE/l ($P=0.002$). In men with MA prolactin levels and prolactinoma volume were higher than in women: 28600 (9450; 63200) *vs* 3400 (1790; 5700) mE/l and 6150 (4100; 12000) *vs* 1880 (870; 3300) mm^3, accordingly. There was no difference between men and women in prolactin levels of NT and MI.

In women of premenopausal age menstrual cycle was regular in 34% of NT, 42% of MI and 4% of MA; in these cases prolactin levels were <3000 mE/l. Women of postmenopausal age accounted 41% of MA and 5–10% of other groups, and prolactin levels were similar in pre- and postmenopausal subgroups. Most found menstrual disturbances were opsomenorrhea (NT 35%, MI 36%, MA 20%) and amenorrhea (NT 13%, MI 16%, MA 76%). Galactorrhea was observed in 21% of NT, 29% of MI, and 19% of MA (including cases of galactorrhea without menstrual disorders), prolactin levels did not differ in patients with or without galactorrhea. Headache and visual disturbances were observed in 50 and 10% of NT, 45 and 14% of MI, 86 and 48% of MA respectively. Prolactin levels $<$ 3000 mE/l were found in most of patients with NT (83%) and MI (85%). There was positive correlation between prolactin levels and prolactinoma volume ($r=0.45$, $P<0.001$). Thus, in our cohort of patients with hyperprolactinemia a portion of nontumoral hyperprolactinemia, microadenomas and macroadenomas was similar. Approximately half of women with nontumoral hyperprolactinemia and microadenomas had normal menstrual cycle with prolactin levels less than 3000 mE/l. In men higher frequency of aggressive macrodenomas was observed.

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P728

Changes of metabolic status in children with acquired and congenital multiple pituitary insufficiency

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Aim

To assess changes of metabolic status in children with pituitary insufficiency.

Methods

We examined retrospectively 28 children with pituitary insufficiency in the Endocrinological department of University hospital (Minsk) over 2001–2013 years. Group 1 (G1) - children with multiple acquired pituitary insufficiency (MAPI) after brain tumors treatment (11 children (73.3%) underwent surgical, 4 (26.7%) - combined treatment: surgical and radiation exposure) ($n=15$; 9.4 ± 0.8 years); Group 2 (G2) - multiple congenital pituitary insufficiency (MCPI) ($n=13$; 12.2 ± 1.1) ($P>0.05$). We examined the levels of total cholesterol (TC), triglycerides (Tr), atherogenicity coefficient (AC), ALT, AST, free thyroxin, TSH, cortisol, ACTH, prolactin, FSH, LH, testosterone, estradiol; height and weight.

Results

Growth retardation were observed in 10 (66.6%) children G1 and 13 (100%) G2 ($P>005$); obesity in 3 (20.0%) children G1 ($P<0.05$). The levels of TC were increased in 5 (33.3%) patients G1 and 1 (7.7%) - G2 ($P<0.05$); Tr - 3 (20.0%) children G1 and 1 (7.7%) G2 ($P<0.05$), AC 3 (20%) G1, 1 (7.7%) G2 ($P<0.05$). G1 children showed the increasing levels of ALT (3(20%)) and AST (3(20%)) children. Hypothyroidism were diagnosed in 100% in both groups ($P>0.05$), secondary hypocorticism 11 (73.3%) children G1 and 4 (30.8%) - G2, diabetes insipidus - 12 (91.7%) and 2 (15.4%) ($P<0.05$), secondary hypogonadism - 3 (20.0%) G1 and 5 (33.3%) G2 ($P>0.05$), GH deficiency - 8 (66.7%) G1 and 13 (100%) G2 ($P>0.05$), hyperprolactinemia in 3 (20%) children G1

Conclusions

The development of multiple pituitary insufficiency (hypothyroidism, secondary hypokorticism, GH deficiency, diabetes insipidus, secondary hypogonadism) were noted in all children with multiple acquired pituitary insufficiency. Alterations in metabolic status (hypercholesterolemia, elevated levels of atherogenicity coefficient) were observed in 8 (53.3%) patients with multiple congenital pituitary insufficiency.

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P729

Poorly differentiated rectal neuroendocrine carcinoma leading to ectopic ACTH syndrome

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Introduction

We present a case investigated due to hypokalemia and diagnosed as rectal neuroendocrine tumor-related EAS.

Case

A 67-year-old woman with weight loss and symptoms of lethargy, abdominal pain was referred due to low serum K^+ levels. Elevated blood pressure and a rectal mass were detected at physical examination. Low serum K^+, elevated ALT levels, lymphopenia, neutrophilia and metabolic alkalosis were present. Computed tomography (CT) revealed asymmetrical rectal wall thickening and multiple masses compatible with metastasis in the liver. Diffuse thickening was present in both adrenal glands and nodules compatible with metastases in lungs. Plasma ACTH at 353 pg/ml was detected. Cortisol was not suppressed in 1 mg and 2-day 2 mg dexamethasone suppression tests (DST) (>75 and 61.9 μg/dl respectively). Circadian rhythm was lost together with elevated overnight serum cortisol levels (>75 μg/dl). Pituitary MR was normal. Cortisol level suppression above 50% was not achieved with high-dose DST. Hypokalemia was thought to be associated with EAS. A biopsy taken from the rectal mass stained positive with chromogranin A, synaptophysin and CD56, while ACTH was negative and was reported as a poorly differentiated neuroendocrine carcinoma. The patient died on the 14th day of admission due to widespread metastatic disease and multiple organ failure.

Discussion

Anorectal neuroendocrine tumors are rare causes of EAS (2%). Hypertension and hypokalemia are findings seen in 70–80% of EAS patients. Optimal treatment of EAS consists of removal of the corticotrophin secreting tumor. However, tumor resection may not be curative in widespread metastatic disease. Since only some cells may secrete ACTH, ACTH may not be stained in biopsy specimens taken from the tumor. While prognosis of small (occult) bronchial carcinoids leading to EAS is quite good, prognosis of extrathoracic neuroendocrine tumors with metastatic disease during diagnosis is generally poor.

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P730

The role of intraoperative hormone levels as predictors of Cushing's disease remission

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Abstract

Transsphenoidal surgery is the treatment of choice for Cushing's disease. Despite the 70–90% remission rates relapses after successful transnasal adenectomy are frequently observed.

Aim

To evaluate the dynamics of intra- and early postoperative levels of adrenocorticotrophic hormone (ACTH) and cortizol and their role as predictors or Cushing's disease remission.

Materials/methods

Fifty patients with Cushing's disease underwent surgery in the Endocrinology Research Centre of Russian Federation. The hormone analyses were provided immunochemiluminiscent method. The blood was taken during the incision of dura mater, then after tumor debulking and then 20 min after it. Then ACTH levels measured 1 day after surgery. In case of early clinical signs of hypocorticism the blood was taken at first day followed by substitution therapy. The criteria of hypocorticism were the ACTH and cortizol levels lower than the nadir.

Results

In postoperative period 82% of patients had adrenal insufficiency (61% at day 0–1, 35% at day 2–4, 5% at day 7), in 10% hormone levels came to normal references, in 8% - stayed higher than reference. The level of hormone (ACTH and cortisol) increased after removal of the tumor (stress release). After 20–min he fell. There are not any dependency between remission and level of hormones during intraoperation research. Only hormone levels at the end of the first day after surgery in 60% showed Cushing's disease remission. That confirmed by 6-months follow-up observation.

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P731

Influence of the exon 3 deletion of GH receptor and IGF1 level at diagnosis on the efficacy and safety of treatment with somatotropin in adults with GH deficiency

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Introduction
Human recombinant growth hormone (hrGH) treatment in adult patients with GH deficiency (GHD) has an important interindividual variability and several factors can influence it. The aims of the study were: i)- to analyze the genotype of GHR regarding exon 3 deletion (d3-GHR) in a serie of adult patients with GHD; ii)- to assess the effect of d3-GHR on initial IGF1 levels; iii)- to evaluate if d3-GHR and/or initial IGF1 levels were associated with adverse effects and/or treatment discontinuation.
Methods
Retrospective study, including 44 patients with adult GHD. Demographic, clinical and biochemical characteristics were evaluated at baseline, at month 6 and 1 and 3 years after hrGH treatment initiation. The d3-GHR was analyzed in 35 patients.
Results
A 37.1% of patients were d3-GHR carriers (31.4% heterozygous) and this situation was not related with IGF1 at baseline. We did not find a significant association between d3-GHR allele and baseline IGF1 ($P=0.14$). Adverse events were more frequent in d3-GHR carriers (30.7 *vs* 18.2% in fl/fl) and in patients with normal IGF1 at diagnosis (43.7 *vs* 17.8% in patients with low IGF1), but this assotiation was not statistical significant. The d3-GHR status was not related with the incidence of adverse events ($P=0.4$) or treatment discontinuation ($P=0.47$). The baseline IGF1 level was neither associated with the development of adverse events ($P=0.08$) nor treatment discontinuation ($P=0.75$).
Conclusions
In our series, the presence of d3-GHR allele was not related with baseline level of IGF1. Neither d3-GHR nor baseline IGF1 level was related with adverse events or treatment discontinuation.

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P732

Hyponatremia in the emergency room of a general teaching hospital: room for improvement

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Introduction
Hyponatremia(HN) is frequent in the emergency room(ER), yet often ignored, or poorly studied/managed. Our objective was to determine the characteristics of patients presenting HN at the ER of a general hospital.
Methods
Retrospective analysis of all 347 patients(AllP) presenting/developing non-translocational HN (serum sodium (SNa) <135 mmol/l) the first 48 h at the Hospital Clinico San Carlos ER in August 2012. Volemia was determined by physical exam, hemodilution *vs* hemoconcentration (urea/creatinine/hematocrit). SNa expressed in mmol/l. SPSS15. Student's t test, χ^2.
Results
A 5.4% of patients with SNa determined presented HN. Of these 33.7% had SNa <130, 0.1% <120. Average age: 60 (s.d. 19); 55.9% (194) were women.19.3% (67) were on SSRI, 10.5% (37) thiazides, 6.9% (24) opiates, 6.9% (24). 13.5% (47) were hypovolemic, 4% (14) hypervolemic, 62% (215) euvolémica (EU), 20.2% (70) undetermined. Physiologic stimuli of AVP were present in most EU, 56.9% presenting pain(EUPAIN). 36.7% (79) of EU had neither pain nor nausea (EUNPH), 16/79 were polydypsic. Plasma/Urine Osmolality were determined in only 7.2% (25), urine electrolytes in 10.1% (35), TSH in 27.3% (92), cortisol in 1.4% (5). AllP Admittance SNa(A-SNa): 131.7 mmol/l (s.d.:3.8), nadir SNa(N-SNa):130.87 (s.d.:3.6). SNa improved in only 124 (35.7%) within 24 h. 41% remained hyponatremic post-discharge (PD). 5% (18) developed overcorrection of SNa (>10 mmol/l at 24 or >18 mmol/l at 48 h). Patients with prior HN (42.1%) had lower A-SNa:129 (s.d.:3.7) *vs* 131.9 (s.d.:2.9) ($P<0.001$), N-SNa(129 (s.d.:3.7) *vs* 131.9 (s.d.:2.9) ($P<0.001$), PD SNa:126.1 (s.d.:4.6) *vs* 131.2 (s.d.:3.3) ($P<0.001$). EUVNPH had lower SNas than the remaining patients AllP-EUNPH) with A-SNa:131.1 (s.d.:3.7) *vs* 132.1 (s.d. 3.8) ($P=0.016$), N-SNa:130.2 (s.d.:4.15) *vs* 131.2 (s.d.:3.28) ($P=0.014$). Principal diagnoses: urinary tract infection:11.8% (41), neoplasia:10.1% (35), HN:4% (14). 6-month ER readmissions rate was higher in EUNPH than in the remaining patients: 45.5 *vs* 27% $P<0.001$).
Conclusions
Most ER hyponatremic patients were euvolemic. Of these a majority were in pain. Euvolemic patients without pain/nausea (many of whom will have undiagnosed SIADH), had more marked HN, and a higher readmissions rate. HN was often persistent and unresolved. Study, diagnosis and treatment of HN were clearly inadequate.

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P733

Prolactinemia and clinical outcome following second generation antipsychotics in early onset schizophrenia

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Introduction
As antipsychotic drugs specifically block the D2 receptors, they induce a certain level of prolactin increase, dependent on the time it takes to dissociate from receptors. A recent review (Besnard *et al*, 2013) mentions that 18% of men and 47% of women treated with antipsychotics for severe mental illness had an increased prolactin level. Even if the long term effects of hyperprolactinemia can be severe, including low bone density, amenorrhea, breast and prostate cancer, new evidence suggests that the increase of prolactin within a certain range under antipsychotic treatment might correlate with a positive evolution in schizophrenic patients.
Methods
Fifteen adolescents aged 14–17, diagnosed with early-onset and very-early-onset schizophrenia according to DSM-IV criteria and KIDDIE-SADS scales were included in the study. They were treated with risperidone 2–4 mg/day. The values of serum prolactine and the PANSS, CGI-S and *CGAS* scores were followed at baseline, 3 months, 6 months and 1 year.
Results
None of the males included in the lot developed symptoms of hyperprolactinemia; part of the included females developed amenorrhea and one had galactorrhea. Serum prolactin levels increased at 3 months, correlated with a decrease in the PANSS score, and then decreased and stabilized to a level higher than baseline at 6 months and 1 year, with no significant differences in the *PANSS* scores within this time frame. The rest of the results are still to be analysed.
Conclusions
The small number of patients is a limitation - studies on bigger populations are necessary and that is why we consider this as a starting point for future research in order to find predictive factors in schizophrenia approach.

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P734

Efficacy of early postoperative radiotherapy for nonfunctioning null cell or silent pituitary macroadenomas

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Background
Suitable postoperative radiotherapy (RT) of nonfunctioning pituitary macroadenomas (NFMAs) is still controversial, subjected to rapid technical and medical progress.

Patients and methods.
We studied 87 patients with NFMA to identify factors affecting tumor control such as the time of RT and tumor pathology. Partial pituitary surgery was performed either by transfrontal (30 patients) or transsphenoidal (57 patients) approach. An immunoperoxidase (avidin biotin technique) analysis for anterior pituitary hormones was performed, revealing 41 null cell adenomas, 22 gonadotropinomas, 13 silent plurihormonal (nongonadotroph) and 11 silent unihormonal adenomas (ACTH, GH or PRL). Tumor recurrence after surgery was defined as a minimum 25% increase of either diameter by serial imaging studies, initially performed at 3 months after surgery and 6 months after RT.
Results
After partial surgery, high voltage RT (mean dose 50.5 Gy) was given to 35 out of 87 patients with a follow-up of 7.5 ± 4.3 years. Recurrence rate was registered in 38% patients (33/52) without RT and 11.4% patients (4/35) after postoperative RT ($P < 0.001$). Tumor relapse in the first year after surgery was noticed in 4/13 silent plurihormonal (nongonadotroph) tumors and in 2/11 silent unihormonal immunoreactive adenomas (for ACTH or PRL) and only in 2/41 null cell and 1/22 gonadotroph adenomas. Immediate postoperative RT showed a significant benefit on the tumor reccurence. Patients who received postoperative RT earlier than one year (18/35) showed a low rate of recurrence, as compared to patients with later RT (χ^2, $P < 0.05$). Regression analysis showed that the early postoperative radiation therapy is independently associated with a lower risk of relapse.
Conclusion
It is tempting to suggest as an optimal time for radiotherapy, the first year post partial-surgery of pituitary macroadenomas. The relapse rate increases gradually along 5 years in patients who were not irradiated.

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P735

Changes in pituitary comorbidities of adult-onset craniopharyngioma depending on date of diagnosis

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Introduction
Craniopharyngioma is an insidious disease that leads to profound comorbidities. Outcomes of the disease have been studied in depth, but there is little data comparing pituitary comorbidities of cases diagnosed in recent years opposed to before. We hypothesized that advances in endocrinologic diagnostics and neurosurgery have led to a lower degree of comorbidities.
Methods
We investigated 54 patients with adult-onset craniopharyngioma (28 male, mean age 40.4 ± 14.2 years) diagnosed between 1965 and 2009 from our institutions' records. We split our cohort in two groups: cases diagnosed after 1997 ('recent') and until that year ('historic'). We compared the presence of pituitary insufficiency between both groups using chi-squared statistics.
Results
Follow-up was 20.0 ± 9.6 and 6.6 ± 4.1 years for historic and recent diagnoses respectively. Both groups (historic: $n = 26$, mean age 34.3 ± 12.3 years; recent: $n = 28$, age 46.1 ± 13.5) did not differ in terms of gender distribution (historic: 14 female, 12 male; recent: 18 femals, 10 males), surgical approach, radiation therapy, pituitary insufficiencies and tumor compression signs before therapy. The historic group had a significantly higher proportion of extrasellar tumor extension (68.2 *vs* 30.8%, $P = 0.01$, OR = 4.8). At last follow-up the historic group had significantly more frequent insufficiencies of the hypothalamic-pituitary axis concerning the adrenal (96.2 *vs* 60.7%, $P = 0.002$, OR = 16.2), thyroid (92.3 *vs* 67.9%, $P = 0.026$, OR = 5.7), somatotropic (92.3*vs* 71.4%, $P = 0.048$, OR = 4.8), and gonadal (92.3 *vs* 64.3%, $P = 0.013$, OR = 6.7) axis. The frequency of diabetes insipidus did not differ between groups ($P = 1.0$). Visual field defects were significantly more common in the historic group (66.7 *vs* 39.3%, $P = 0.049$, OR = 3.1).
Conclusion
We found significant differences in post-operative pituitary insufficiencies and visual field defects between patients diagnosed before and after 1997. This might be a consequence of improved surgical approach. Furthermore, differences in tumor extension could be due to improvements in diagnostics and earlier treatment of craniopharyngioma.

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Nuclear receptors and signal transduction

P736

Formation of progesterone receptor-NF-κB complex is required for progesterone-induced NF-κB nuclear translocation and binding onto the p53 promoter

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We previously showed that progesterone (P4) regulates p53 expression and cell cycle progress in human umbilical venous endothelial cells (HUVEC) through progesterone receptor (PR) activation of extra-nuclear signaling pathways. Here, we showed that P4 activated the PR and hence increased the formation of progesterone receptor A-(PR-A)-NF-κB complex in both the cytosol and the nucleus. Chromatin immunoprecipitation demonstrated an interaction between PR and the NF-κB binding motif on the p53 promoter. Ablation of the NF-κB binding motif on the p53 promoter completely abolished the P4-increased p53 promoter activity. In the absence of P4, over-expression of NF-κB did not cause NF-κB nuclear translocation. Blockade of PR abolished the P4-induced NF-κB nuclear translocation in the NF-κB-overexpressing HUVEC. These results uncover a novel role of PR for P4-induced NF-κB nuclear translocation and p53 up-regulation and suggest that PR-A-NF-κB complex is required for NF-κB nuclear translocation and binding onto the p53 promoter. The findings from the present and our previous studies suggest that both nuclear PR and non-nuclear PR are involved in the P4-regulated p53 expression and cell cycle progress.

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P737

The effect of hormone-induced PtdIns (4, 5) P_2 depletion on endocytosis suggests the importance of local regulation of inositol lipid signalling

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Receptor endocytosis plays an important role in regulating the responsiveness of cells to specific hormones. Phosphatidylinositol 4, 5-bisphosphate (PtdIns(4, 5)P_2) has been shown to be critical for many endocytic processes including the internalization of G protein-coupled receptors (GPCRs). We have previously shown that depletion of PtdIns(4, 5) P_2 by the chemically induced plasma membrane recruitment of a 5-phosphatase domain prevents the internalization of the β_2 adrenergic receptor (β_2AR), as measured by its interaction with the early endosome marker Rab5. In this study we tested the effect of hormone-induced PtdIns(4, 5) P_2 depletion on β_2AR internalization with the help of type 1 angiotensin receptor (AT_1R).
We used luciferase-labelled β_2AR and fluorescently tagged Rab5 to follow the endocytic route of the receptors in HEK-293T cells using bioluminescence resonance energy transfer (BRET). To reduce plasma membrane PtdInsP_2 levels, we either applied our previously developed rapamycin-inducible heterodimerization system or we used wild type (wt) and internalization-incompetent mutant (Δ319 and TSTS/AAAA) forms of the G_q protein-coupled AT_1R which degrades PtdIns(4, 5) P_2 through the activation of phospholipase Cβ. We even created and tested an AT_1R fusion protein that is capable of both the rapamycin-induced and the hormone-activated depletion methods. We measured the rate of PtdInsP_2 depletion with the help of the PtdIns(4,5)P_2-binding PH domain of phospholipase Cδ_1.
Confirming our previous results, β_2AR internalization was inhibited after PtdIns(4, 5) P_2 depletion by our rapamycin-based system. A similar inhibition occurred after the activation of wt AT_1R. However, PtdIns(4, 5) P_2 depletion by internalization-incompetent AT_1R forms caused very little inhibition of β_2AR internalization, despite the higher rate of lipid depletion compared to the wt receptor.
Our data suggest that wt AT_1R might inhibit β_2AR internalization by competition for the endocytic machinery, and that the effect of plasma membrane PtdIns(4, 5) P_2 depletion on β_2AR internalization can be different depending on the method of lipid degradation, implying that distinct PtdIns(4, 5) P_2 pools might be required for endocytosis and receptor activation.

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P738

Thyroid receptors antagonizes TGFβ actions in vivo and in culture cells

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Transforming growth factor beta (TGFβ), which plays a key role in cancer and fibrotic disorders, mediates its actions mainly through activation of Smad transcription factors, which bind to Smad Binding Elements (SBEs) in target genes. We have previously observed that the thyroid hormone T_3 blocks transactivation of SBE-containing reporter plasmids by TGFβ, and represses transcription of endogenous TGFβ target genes. We have now analysed the thyroid hormone receptor (TR) isoform as well as the receptor domains responsible for this transcriptional antagonism. In GH4C1 pituitary cells, the TRβ specific agonist GC1 is as potent as T_3 to repress SMAD-dependent transactivation, showing that this isoform mediates the antagonism. However, expression of TRα in other cell types also mediates repression of TGFβ-dependent transactivation by T_3. Therefore, both receptor isoforms can antagonize TFGβ actions. Using TRα and TRβ mutants we observed that the receptor DNA binding domain (DBD) is essential to carry out the repressive effect, whereas the ligand-dependent transcriptional activation domain responsible for coactivators binding appears to be dispensable. We also detected a direct interaction of TRα and TRβ with Smad 2/3 and Smad 4. The DBD plays an important role in this interaction, which is reversed by T_3. In chromatin immunoprecipitation (ChIP) assays with SBE-containing promoters, T_3 inhibits TGFβ-dependent recruitment of Smads. TRs bind to the SBE-containing regions and this interaction is also released by T_3. We had observed that hyperthyroidism alleviates the fibrotic response induced by bleomycin in mice skin. We have now examined if TR signalling could also impact liver fibrogenesis. Indeed, 18-month-old knock-out mice lacking TRαand TRβ exhibited a spontaneous injury phenotype with increased collagen deposition, demonstrating that the endogenous receptors play a role *in vivo* as inhibitors of this TGFβ-dependent response.

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P739

Increased irisin abundance in muscle and blood circulation after treadmill exercise in mice

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The myokine irisin is secreted after cleavage of the transmembrane protein Fibronectin type III domain-containing protein five and was shown to induce a thermogenic program in white adipose tissue. This cleavage can be induced by exercise, thus linking exercise with browning of adipose tissue. We investigated the response of Fndc5/irisin as well as its inducer Peroxisome proliferator-activated receptor gamma co-activator 1α (Ppargc1a) in mice long-term selected for high treadmill performance. Male mice were randomly assigned to either a sedentary control group (CO), a group with free access to a running wheel (RW), or a treadmill exercise group (TM). mRNA and protein abundances of Fndc5 and Ppargc1a in muscle tissue as well as presence of irisin in blood and muscle were investigated. Western blot analyses were performed using antibodies being able to differentiate between irisin at ∼12 kDa and full-length Fndc5 at ∼25 kDa. Irisin abundance was significantly higher in muscle and serum of TM group mice immediately after exercise. Compared to the CO group, mRNA expression of transcripts 3 and 4 of Ppargc1a was up-regulated in the TM group (33- and 9-fold respectively). However, *Fndc5* mRNA remained unchanged immediately after exercise. Furthermore, neither Fndc5 nor Ppargc1a protein was elevated in muscle tissue. The Ppargc1a-Fndc5/irisin pathway did not clearly respond to mild exercise in the RW group. Our results indicate that irisin cleavage and secretion increases rapidly after acute but not after moderate voluntary exercise in our mouse model. The relatively high basal level of irisin in skeletal muscle and serum indicates a constant, physiological Ppargc1a-independent irisin production and secretion. Ppargc1a induction as well as irisin production and secretion in response to acute exercise may be involved in the metabolic adaptation to high endurance capacity.

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Obesity

P740

Bariatric surgery in Prader–Willi syndrome

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Introduction
Obesity-related complications are the main causes of morbidity and mortality in Prader–Willi syndrome (PWS) patients. We report a case of a 17-year-old patient with PWS who had metabolic complications of poorly controlled diabetes mellitus (HbA1c 8.3% on 56 units of insulin daily) and obesity (BMI 33 kg/m^2). He underwent laparoscopic assisted duodenal switch but unfortunately died from aspiration pneumonia 3 days after surgery. A literature search was conducted to review the various surgical techniques, long-term outcomes and the recurrence rates of obesity after each procedure in these patients.
Results
The bariatric procedures performed will be presented. Among individuals with PWS, 37% underwent biliopancreatic diversion (BPD), 29% Roux-en-Y gastric bypass (RYGBP), 18% intragastric balloon, 6% vertical banded gastroplasty (VBG), 3% biliopancreatic diversion with duodenal switch (BPPDS), 3% jejunoileal bypass (JB), 1.5% truncal vagotomy, 1.5% adjustive silicon gastric banding (ASGB).
Restrictive bariatric surgery, such as gastric banding or bypass, has not been shown to reduce hyperphagia or achieve long-term weight reduction. In fact, it is associated with unacceptable morbidity and mortality. On the other hand, BPD and BPPDS were reported to result in successful weight loss but there were frequent complications from the resulting intestinal absorption. Roux-en-Y gastric bypass (RYGBP) appears to have better long-term results in terms of sustained weight loss but with a high rate of revision of gastric pouch.
Conclusion
Although case reports and small case series have documented good improvement in metabolic profile and weight loss with bariatric surgery in PWS, there is a paucity of data on long-term effects.

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P741

Effects of depressive symptoms on clinical outcomes, inflammatory markers and quality of life after a significant weight loss in a bariatric surgery sample

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Background and aims
Obesity is linked to a low-grade and chronic systemic inflammation that improves after a significant weight loss. In the same way, depressive disorder has been suggested to be associated with systemic inflammation up regulation. We aimed to explore whether, after a significant weight loss, the presence of depressive symptoms was associated with differences in terms of inflammatory markers and quality of life compared with individuals without significant depressive symptoms.
Material and methods
Sixty patients (78.3%♀, age 46.35±9.89 and months since BS 46.28±18.1) who underwent BS, with a minimum follow up of 18 months, were evaluated cross-sectionally. Initial and current BMI, comorbidity, sociodemographic and biochemical parameters were recorded. For the screening of depression, the Beck Depression Inventory (BDI) was administered. A score in BDI >16 was considered as positive for significant depression.
Results
At the time of the evaluation, ten subjects (16.6%) had a positive screening for depressive disorder. The percentage of patients with weight regain was greater among subjects with symptoms of depression (70 *vs* 32%; $P=0.024$) compared with subjects without significant depressive symptoms, although no differences were seen between the two groups regarding BMI prior to surgery and current BMI. Acute phase reactants were all significantly higher among subjects with positive screening for depression compared to normal individuals: platelet count (319 300±15 212×10^9/l *vs* 231 700±46 794×10^9/l; $P=0.001$), erythrocyte sedimentation rate (24.7±11.28 *vs* 16.64±10.29 mm; $P=0.03$), fibrinogen (486±107 *vs* 406±66 mg/dl; $P=0.003$), ferritin (105.5±179.7 *vs* 33.74±44.12 ng/ml; $P=0.014$) and ultrasensitive C-reactive protein (0.96±1.84 *vs* 0.24±0.26 mg/dl; $P=0.008$). Also, all domains of quality of life were significantly lower in the depressive group.

Conclusions
Despite a significant weight loss, inflammatory markers are greater and quality of life lower when associated with depressive symptoms.

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P742

Clinical associations of perceived well-being in obese subjects: a focus on laboratory measurements

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Aims
To document clinical associations of perceived well-being (PWB) in obese subjects
Methods
Prospectively collected 'Obesity Polyclinic' database was retrospectively analyzed for the answers of the questionnaries fullfilled during the initial evaluation for obesity. After exclusion unavailable cases, the answers to the question '*how do you describe your general health/well-being?* i) *very well* ii) *well* iii) *not bad* iv) *bad* v) *too bad*' each were categorized, and these groups were compared for BMI per se, total body fat content, waist–hip ratio, fasting plasma glucose, HOMA-IR, LDL-C, HDL-C, TSH, anti-thyroid peroxidase, free thyroxine, hemoglobin, creatinine, transaminases, 25(OH)D, albumin levels. As a secondary analysis, the associations of the symptoms with the PWB were examined.
Results
During the study period, who satisfied the inclusion criteria, 623 subjects (M/F: 69/554, median 42-year-old with a BMI of 34.6 kg/m^2) had had completed the initial evaluation form. The distribution of answers to PWB was as 89 (14.3%) well, 269 (43.2%) not bad, 229 (36.7%) bad, and 36 (5.8%) too bad. Nervousness, sleep disturbances, headache, depressive mood, lassitude correlated with PWB. The curve estimation demonstrated independent associations of increasing PWB scores with higher levels of 25(OH)D, albumin, and HDL-C, but no association with HOMA-IR or presence of metabolic syndrome or TSH or anti-thyroid peroxidase levels. Further, both 25(OH)D and albumin levels associated with the number of symptoms also (i.e. 68.8% of subjects with 25(OH)D levels $\geqq$30 ng/ml had 0–1 symptom, 25.0% had 2–3 symptoms, and 6.2% had 4–5 symptoms; whereas this distribution in subjects with 25(OH)D levels $<$20 ng/ml was as: 33.2% had 0–1 symptom, 33.6% had 2–3 symptoms, 33.2% had 4–5 symptoms, $P=0.006$; similar distribution differences were observed between albumin level groups).
Conclusions
Serum 25(OH)D and albumin levels are associated with PWB and with the symptoms frequently encountered in obese subjects.

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P743

Profile of patients treated in our 'eating disorders unit' from 1996 to the present

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Rationale
Our aim has been to describe the assistance demand and the profile of patients treated in the eating disorders unit in our hospital.
Methods
Observational retrospective study (reviewing medical histories).
Results
One thousand two hundred and fourteen patients have been treated at the eating disorders unit between 1996 and 2012, 91.8% female. Age at first visit: 22.1$\pm$8.3 years. Time of monitoring tracking: 1.2$\pm$1.8 years.
The Diagnoses according to CIE-10 criterions were: anorexia nervosa (AN) 42.5%, atypical AN 14.0%, bulimia nervosa (BN) 20%, atypical BN 3.8%, other diagnoses 19.7%.
Comparing the diagnoses BN and AN, the age of patients at first visit was 20.4$\pm$6.5 *vs* 23.3$\pm$7.9 years ($P<0.001$) and follow-up time was 1.7$\pm$2.3 *vs* 0.7$\pm$1.3 years ($P<0.001$). In males, atypical forms were more prevalent.
The demand for care at the unit was higher between 1997–2004 (average 93 new patients per year) compared to 2005–2012 (average of 46 new patients per year). Half of the patients were discharged evaluated for cure (about 90% of those who completed the intervention program), while the 42.5% left the program.
Conclusion
The most common type of eating disorder referred to our unit is anorexia nervosa (56.5%). In anorexia nervosa, the age of the patients at first visit was lower and the time of monitoring tracking at our unit was higher compared to bulimia nervosa. In the last decade, the incidence of demand was reduced to half, remaining constant in recent years.

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P744

The mRNA levels of TNFα, Omentin-1 and PPARγ in adipose tissue of patients with abdominal obesity

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Adipose tissue is a complex, essential, and highly active metabolic and endocrine organ that release a large numbers of bioactive mediators (adipokines). Obesity is defined as an excessive growth of adipose tissue. As such, it is likely that adipokines could play an important role in the development of diseases associated with obesity including insulin resistance, inflammation, hypertension, cardiovascular risk and metabolic disorders. PPARγ is a ligand-activated transcription factors that is implicated in adipocyte differentiation, function and influence on adipokine gene expression.
The aim of our work was to estimate the TNFα, *Omentin-1* gene, PPARγ mRNA levels in visceral fat of patients with abdominal obesity and controls.
We generated the visceral fat of 23 patients with abdominal obesity (mean age 45$\pm$8 years, 4 males, mean BMI 34.7$\pm$8.5) and 7 controls (mean age 42.1$\pm$10 years.8, 5 males, BMI 24.0$\pm$2.6). Visceral fat was received from gastrocolic omentum during laparoscopic cholecystectomy in non-acute period of gall-stone disease. TNFα, PPARγ, *Omentin-1* gene mRNA levels were estimated by RT-PCR with TaqMan probes. G protein mRNA levels (GNB2L1) was used as internal control.
Difference in TNFα, Omentin-1 gene, PPARγ mRNA levels between patients with abdominal obesity and controls was not statistically significant ($P>0.05$). Spearman correlation analysis showed positive correlation between PPARγ mRNA levels and Omentin-1 mRNA levels ($r=0.552$; $P=0.033$) in patients with abdominal obesity in visceral fat.

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P745

The efficacy and safety of 12 weeks Anethum graveolens on waist circumference and triglyceride in patients with metabolic syndrome

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Introduction
High waist circumference and triglyceride (TG) disturbances are two important and diagnostic components constituting the metabolic syndrome. This study was designed to investigate whether herbal medicine, Anethum graveolens (dill) extract, is capable to improve abdominal obesity presented by high waist circumference and triglyceride in patients with metabolic syndrome.
Design
A total of 24 mens and womens who met the criteria of metabolic syndrome (updated of ATP3) were included. A permuted block randomization was used to achieve a balance between treatment groups. Each group received either *Anethum graveolens* extract (dill group; $n=12$) or placebo (control group; $n=12$), one pill (600 mg) every day for 3 months.
Results
At the end of 12 weeks, mean waist circumference did not change significantly from baseline in both groups and these measures also did not differ between the two treatment groups. In contrast, a remarkable statistically and clinically improvement in the mean TG level was observed from 257.0 (124.5) at baseline to 201.5 (115.5) at the end of study in dill group. However serum TG was not significantly different in dill group compared with placebo. No adverse reaction was detected during the course of this study.

Conclusions
The beneficial effect of 12 weeks dill treatment include the improvement of triglyceride level from baseline was not accompanied by changes in abdominal obesity presented by waist circumference. It seems that larger human trials should be performed to investigate the clinical efficacy and safety of dill treatment as an herbal medicine to resolve metabolic syndrome related criteria.
Keywords:
Abdominal obesity, waist circumference, metabolic syndrome, Anethum graveolens (dii)
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P746

Modification in the expression of peripheral appetite signals during hypoxia exposure contributes to anorexia

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Introduction
Anorexia, one of the major problems at high altitude caused by alterations in adipose, gut and pancreatic hormones responsible for appetite regulation and energy balance may be alleviated by understanding the changes during hypoxia. The present study was aimed to elucidate the response of peripheral tissues to hypobaric hypoxic exposure in terms of circulating levels and expression pattern of appetite regulatory hormones, adipose cell morphology and glucose regulation.
Methodology
Male Sprague–Dawley rats were exposed to hypobaric hypoxia at a simulated altitude of 7620 m in a hypobaric chamber for different duration up to 7 days.
Results
Hypoxia exposure caused reduction in food intake and body weight. Plasma leptin levels initially increased and decreased to normal at 24 h of hypoxia. Circulating levels of ghrelin, resistin, insulin and glucose increased while CCK, GLP1 and PPY decreased during hypoxia. Decrease in adipocyte size was observed during hypoxia. Increased resistin, GRP78 expression and decreased leptin, IL6, Caspase12, PGC1β expression in adipose tissue was observed during hypoxia. Adiponectin mRNA decreased in adipose tissue while there was no change in protein levels. Stomach ghrelin and ghrelin receptor expression increased while CCKAR, PPARα and PPARδ expression decreased during hypoxia. Liver CCKAR, PPARδ and Caspase12 decreased while GRP78, PPARα and PGC1α increased during hypoxia.
Discussion and conclusion
Increase in both glucose and insulin levels indicate insulin resistance. Increased GRP78 shows onset of endoplasmic reticulum (ER) stress in adipose tissue. Decreased PGC1β shows halt of adipogenesis and weight loss is due to reduction in adipose cell size. In conclusion hypoxia impairs peripheral tissues response by altering expression of appetite regulatory hormones, reducing adipocyte size, impairment in glucose clearance and inducing ER stress which altogether might be a few causative factors for anorexia.
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P747

Accumulation of abdominal fat in relation to selected proinflammatory cytokines concentrations in non obese Wrocław inhabitants

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Introduction
Metabolically obese normal weight (MONW) subjects, despite their normal BMI, present metabolic disturbances characteristic of abdominal obesity. One of the reasons might be subclinical inflammation caused by the fat tissue excess. The aim of the study was to asses the association between accumulation of fat (especially abdominal) and concentration of selected proinflammatory cytokines – interleukins (IL-6, IL-18) and C-reactive protein (CRP).
Methods and procedures
The study population consisted of 342 subjects (218 womens, 124 mens; age 20–40 years, BMI <27 kg/m^2) recruited from a community center in Wroclaw. The group was divided based on the homeostasis assessment insulin resistance index (HOMA) value: 90 MONW subjects with HOMA >1.69 and 252 subjects as control group. Anthropometric parameters, serum IL-6, IL-18, CRP, glucose, insulin concentrations and insulin sensitivity/resistance indexes were evaluated.
Results
CRP levels were significantly higher (3.26 vs 1.97, $P=0.03$) in MONW women than in the control group. Serum IL-6, IL-18 levels in males and females did not differ in both groups. IL-6 showed significant correlation with the abdominal to gynoidal fat tissue deposit ratio in women. There was a correlation between the CRP and BMI, WHR, waist circumference, total fat, abdominal fat deposit and abdominal to gynoidal fat deposit ratio in both sexes. In women, a positive correlation between CRP and HOMA, FIRI and negative with QUICKI index was present.
Discussion
Increased accumulation of abdominal adipose tissue in non-obese, young and healthy subjects alike is related to increased CRP levels. This might be one of the causes of accelerated atherosclerosis and its clinical consequences in MONW subjects.
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P748

Bariatric surgery and bone loss: novel mechanisms and comparison of different modalities

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Although bariatric surgery is the most effective weight loss therapy, its skeletal consequences are unclear. The aim of this study was to assess the impact of weight loss, gut hormones, adiponectin on bone loss in people undergoing Dieting (Diet), Gastric Banding (GB) and Gastric Sleeve (GS) over 24 months post-intervention.
There were 15 Diet, 8 GB and 20 GS subjects with mean ($\pm$s.d.) age 53 (12) years and BMI 39 (6). At 12 months mean ($\pm$s.d.) % weight change was Diet – 4.5 (5), GB – 12 (6), and GS – 26 (8), $P<0.0001$. Bone loss (total hip (TH), %) was -0.86 (1.6) in Diet and -1.6 (1.5) in GB. For GS maximal weight loss occurred in the first 6 months but bone loss continued: 3.5 (2) % at 6 months, 6.1 (3) % at 12 months, $P<0.0001$. The mean postprandial PYY % ($+90$ min) response differed between groups: Diet 58 (102), GB 70 (74), GS 150 (106), $P<0.0008$. Adiponectin change (%) varied between groups: Diet 4 (22), GB 21 (19), GS 75 (62), $P=0.0022$ without significant GLP-1 change. Bone turnover markers increased only in GS with osteocalcin by 110 (89)% and uNTX by 89(83) %, $P<0.001$. Calcium intake, vitamin D and PTH were normal throughout.
For all study patients at 12 months their BMD loss correlated significantly with weight loss, postprandial PYY and adiponectin. In the multivariate analysis weight loss and PYY response explained 56% of TH BMD loss ($P<0.0001$).
GS patients with 24 months data ($n=12$) had ongoing 9 (3) % TH BMD loss, $P<0.001$ despite no further weight loss.
GS was the most efficient weight loss modality. However, there was evidence of ongoing bone loss in GS not explained by weight loss alone and associated with postprandial PYY and adiponectin changes. These findings have significant implications for people undergoing bariatric surgery and longer term studies of bone health are needed.
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P749

The effects of octreotide acetate long-acting repeatable (LAR) on mean platelet volume in acromegaly: octreotidelar may have a detrimental effect on MPV, a new indicator of atherosclerosis

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Introduction and objective
Cardiovascular mortality is high in acromegaly. Our aim in this study was to determine the levels of the new cardiovascular marker in active acromegaly patients, the mean platelet volume (MPV) values before and after octreotide acetate LAR treatment.
Material and methods
Thirty-six patients with active acromegaly who presented at the endocrinology department (mean age 46.0±14.0 years and mean BMI: 30.4±5.1 kg/m^2) and 30 age- and BMI-matched (mean age 46.4±12.5 years; mean BMI: 31.7±8.1 kg/m^2) healthy individuals were included in the study. All complete blood count (CBC) analysis was performed with the automatic hematology analyzer Beckman Coulter LH 750 (Beckman Coulter, USA). The platelet count (PC), mean platelet volume (MPV), platelet distribution width (PDW) and plateletcrit (PCT) were evaluated. The differences between before and after treatment values were analyzed with the paired *t*-test. The independent *t*-test was used for the comparison of patient and control groups. Relationship between variables was evaluated with Pearson's correlation test. A P value less than 0.05 was considered statistically significant.
Results
Serum MPV levels in acromegalic patients were not different from control subjects before treatment (7.9±0.8 and 7.9±0.9 fl respectively). Serum MPV values increased significantly in the acromegalic patients after treatment (8.3±0.9 fl, $P=0.047$) and differed from control subjects. MPV in acromegalic patients showing remission or cure was significantly higher than control subjects after the treatment. No statistically significant differences were found between the other parameters such as hemoglobin, platelet count, WBC count, Hgb, Hct, PCT, and PDW.

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P750

Leptin evolution in Aves

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The discovery of leptin in 1994 has opened a new era in the study of energy balance control at the molecular level. By informing the brain and other tissues the state of fat stores, leptin plays a key role in the control circuits of both appetite and energy expenditure, thus affecting most if not all of the body's activities. This discovery in mammals stimulated a great interest in the physiological role and molecular mechanism of leptin in chickens. However, a true chicken leptin ortholog could not be found despite of our finding of the chicken leptin receptor (cLepR). In addition to the inability to detect leptin-like sequences in genomic, transcriptomic and proteomic analyses, also circulating leptin activity could not be detected in chickens, using a bioassay which is based on the cLepR. Moreover, injection of a highly potent leptin receptor antagonist had no effect in chickens. All these observations have now gained a further support by our new finding of a true leptin ortholog in recently deposited genomic sequences of doves (Columba livia) and several other birds. Further study in doves demonstrated expression of leptin mRNA primarily in liver and gonads and also indicated leptin bioactivity in the dove circulation. Therefore, these findings provides a new opportunity for the study of energy balance control by comparing birds that have lost or retained the leptin gene and for understanding the control of energy homeostasis, at an evolutionary perspective.

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P751

Level of knowledge about type 1 diabetes mellitus among nurses employed at endocrinological dispensaries

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Background
Osteocalcin, a marker of bone formation, is also known as a regulator of glucose and fat mass. The purpose of this study was to determine the association between obesity, metabolic risks and serum osteocalcin in postmenopausal women.
Methods
We selected 214 postmenopausal women and determined serum osteocalcin, fasting plasma glucose (FPG), fasting insulin, high-sensitivity C-reactive protein (hs-CRP), the homeostasis model assessment of insulin resistance (HOMA–IR), lipid profile, and anthropometric values (BMI, waist-to-hip ratio (WHR), body fat, and visceral fat area (VFA).
Results
After adjustment for age and years since menopause, WHR and VFA were negatively correlated with serum osteocalcin, but BMI did not show a significant correlation. Serum osteocalcin was negatively correlated with fasting insulin and HOMA–IR, but FPG, lipid profile, and blood pressure did not show a significant correlation. Based on multiple regression analysis, age and HOMA–IR were the most important predictors of osteocalcin.
Conclusion
Our study showed that serum osteocalcin has some significance as an indicator of metabolic risk, including abdominal obesity and insulin resistance. Bone as well as adipose tissue may be an active organ that regulates energy metabolism. A larger study will be needed to clarify the potential of osteocalcin as an indicator of cardiovascular disease.

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P752

Adiponectin upregulates SHBG production: molecular mechanisms and potential implications

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Epidemiological studies have shown that plasma SHBG levels correlate with plasma adiponectin levels, both in men and women. To the best of our knowledge there are no reports describing any molecular mechanism by which adiponectin regulates hepatic SHBG production. The aim of the present study is to explore whether adiponectin regulates SHBG production by increasing HNF-4α levels through reducing hepatic lipid content. For this purpose, *in vitro* studies using human HepG2 cells, as well as human liver biopsies were performed. Adiponectin treatment increased SHBG production *via* AMPK activation in HepG2 cells. Adiponectin treatment decreased the mRNA and protein levels of enzymes related to hepatic lipogenesis (ACC) and increased those related to fatty acid oxidation (ACOX and CPTI). These adiponectin-induced changes in hepatic enzymes resulted in a reduction of total TG and FFA and an increase of HNF-4α. When HNF-4α expression was silenced by using siRNA, adiponectin-induced SHBG overexpression was blocked. Furthermore, adiponectin-induced upregulation of SHBG production *via* HNF-4α overexpression was abrogated by the inhibition of fatty acid oxidation or by the induction of lipogenesis with a 30 mM glucose treatment in HepG2 cells. Finally, adiponectin levels correlated positively and significantly with both HNF-4α and SHBG mRNA levels in human liver biopsies. Our results suggest that adiponectin increases SHBG production by activating AMPK which reduces hepatic lipid content and increases HNF-4α levels.

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P753

Correlates of visceral and subcutaneous fat thickness in non-diabetic obese and morbidly obese patients

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Objective
To determine the correlates of visceral and subcutaneous fat thickness in non-diabetic obese and morbidly obese patients.
Methods
A total of 31 obese female outpatients composed of morbidly obese ($n=16$, BMI of ≧40 kg/m^2) and obese ($n=15$, BMI of 30–39.9 kg/m^2) patients were included in the present study. Data on age, anthropometrics, blood biochemistry, HOMA–IR,

carotid intima-media thickness (CIMT) were recorded in each subject as were plasma resistin (μg/l) and visfatin (μg/ml) levels, epicardial, subcutaneous and abdominal fat thickness (mm). Correlates of visceral and subcutaneous fat thickness were determined *via* linear regression models with inclusion of severity of obesity, insulin resistance, plasma resistin and visfatin levels and CIMT as variables.
Results
Epicardial fat thickness (mm) was 3.1 (1.0–10.20) and 8.8 (2.60–13.0), CIMT (mm) was 5.8 (4.7–8.9) and 5.9 (4–8.6), abdominal fat thickness (mm) was 10.8 (7.8–16.1) and 13.2 (8.7–16.5), subcutaneous fat thickness (mm) was 43.8 (28.4–62.9) and 57.4 (39.5–72.7), plasma resistin levels (μg/l) were 8.5 (4.7–38.1) and 10.8 (0.7–26.4) and plasma visfatin levels (μg/ml) were 55.5 (5.1–209.5) and 78.2 (4.7–228) in obese and morbidly obese patients respectively. Linear regression analysis revealed that being morbidly obese was likely to increase epicardial fat thickness by 4.33 mm ($P=0.004$) compared with obesity, while for each 1 unit increase in HOMA levels, subcutaneous fat thickness was likely to decrease by 1.16 mm ($P=0.009$).
Conclusion
In conclusion, our findings revealed that neither plasma levels for resistin and visfatin nor CIMT correlated with visceral or subcutaneous fat thickness in non-diabetic obese males, while increase in subcutaneous and epicardial fat thickness values were noted with decrease in HOMA-IR and the presence of morbid obesity respectively.
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P754

Meaningful and sustained weight loss and improvement of lipid profile in hypogonadal men on long-term treatment with testosterone undecanoate (TU) injections are independent of age: observational data from two registry studies

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Introduction
Improvements of anthropometric and metabolic parameters on long-term testosterone replacement therapy (TRT) from our registry studies have been reported in 2013 (Saad, Obes; Yassin and Doros, Clin Obes; Traish, Int J Clin Pract).
Methods
Five hundred and sixty-one hypogonadal men from both registry studies were divided into age groups ≤65 (Group A, $n=450$) and >65 years (Group B, $n=111$). All men were treated with 3-monthly TU injections for up to 6 years.
Results
Mean weight (kg) decreased from 102.52±15.56 to 90.15±9.69 in Group A and from 102.83±15.64 to 95.35±9.03 in Group B. Model-adjusted mean change from baseline was −14.78±0.35 and −15.14±0.71 kg respectively. Percent change from baseline was −13.56±7.56% in Group A and −13.28±7.14% in Group B. Waist circumference (cm) decreased from 106.54±9.03 to 98.26±7.1 in Group A and from 108.95±10.75 to 100.72±9.45 in Group B. The mean change from baseline was 9.34±0.2 cm in Group A and 10.45±0.47 cm in Group B.
BMI (kg/m^2) decreased from 32.58±5.08 to 29.02±3.01 in Group A and from 32.84±4.86 to 30.35±2.61 in Group B. The mean change from baseline was −4.72±0.11 and −4.81±0.22 kg/m^2 respectively ($P<0.0001$ for all).
Total cholesterol (TC, mg/dl) decreased from 268.92±45.95 to 193.56±16.58 in Group A and from 268.44±52.69 to 191.69±21.8 in Group B, LDL (mg/dl) from 159.87±36.7 to 119.81±34.87 in Group A and from 162.48±31.63 to 120.86±33.56 in Group B, triglycerides (mg/dl) from 262.35±73.16 to 192.1±34.4 in Group A and from 266.9±84.37 to 192.27±32.16 in Group B. HDL (mg/dl) increased from 48.91±17.33 to 59.55±17.66 in Group A and from 51.64±16.56 to 61.99±16.87 in Group B. TC:HDL ratio improved from 6.15±2.42 to 3.54±1.04 in Group A and from 5.67±2.09 to 3.32±0.91 in Group B ($P<0.0001$ for all).
Conclusions
TRT in hypogonadal men resulted in meaningful and sustained weight loss and improvement of lipid profile independent of age.
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P755

Anthropometric and metabolic parameters in 46 hypogonadal men with obesity grade III improve upon long-term treatment with testosterone undecanoate (TU) injections: Observational data from two registry studies

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Introduction
Numerous studies have reported inverse associations between testosterone and obesity as well as other components of the metabolic syndrome.
Methods
From two registry studies of 561 hypogonadal mens, 46 mens with obesity grade III (BMI ≧40 kg/m^2) were selected. All patients received TU injections for up to 6 years. 46 mens were followed for 2 years, 43 for 3 years, 37 for 4 years, 34 for 5 years, and 24 for 6 s. Declining numbers are result of the registry design.
Results
Weight (kg) decreased from 129.02±5.67 to 103.33±4.17, mean change from baseline −27.15±0.74 kg, percent change from baseline −20.99±3.16%.
Waist circumference (cm) decreased from 118.41±5.69 to 106.48±4.91, mean change from baseline 12.44±0.36 cm. BMI (kg/m^2) decreased from 41.93±1.5 to 33.62±1.58, mean change from baseline −8.79±0.23 kg/m^2.
Mean fasting glucose (mg/dl) decreased from 115.48±23.85 to 96.54±2.9 ($P<0.0001$), mean change from baseline −18.48±2.96 mg/dl, HbA_{1c} (%) from 7.57±1.38 to 6.08±0.5, mean change from baseline −1.61±0.13%.
Total cholesterol (TC; mg/dl) decreased from 306.76±43.03 to 192.23±9.17 (<0.0001), LDL (mg/dl) from 190.57±36.6 to 136.24±28.07 ($P<0.0001$), triglycerides (mg/dl) from 326.87±60.21 to 194.4±12.59 ($P<0.0001$). HDL (mg/dl) increased from 62.76±18.7 to 72.55±13.34 ($P<0.0001$). The TC:HDL ratio declined from 5.47±2.57 to 2.75±0.59 ($P<0.0001$). Systolic blood pressure (mmHg) decreased from 161.04±14.3 to 142.05±9.57, diastolic blood pressure from 97.07±10.91 to 80.89±6.76.
Liver enzymes AST and ALT (U/L) decreased from 42.39±17.84 to 20.33±1.9 and from 43.52±20.68 to 20.43±2.75 respectively ($P<0.0001$ for both), suggesting a reduction in liver fat content.
C-reactive protein (CRP, mg/l) declined from 3.96±4.31 to 0.57±0.59 ($P<0.0001$).
There were no drop-outs.
Conclusions
All changes were in a clinically meaningful magnitude and sustainable for the full observation period. TRT seems to be an effective approach to achieve sustained weight loss in excessively obese hypogonadal men.
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P756

Unstandardized meal does not affect plasma concentrations of leptin, acylated and des-acylated ghrelin in humans

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Background
Leptin and both forms of ghrelin (acylated and des-acylated) are peptide hormones involved in appetite control and food intake regulation in humans. It has been thought that circulating ghrelin concentrations are elevated by fasting and suppressed following a meal, whereas leptin concentrations change in the opposite direction. Most studies, however, only examined these changes after a standardized meal and at different points in time.
Objective
The aim of the present study was to investigate whether plasma concentrations of leptin, acylated and des-acylated ghrelin measured in healthy individuals are different before and short term after an unstandardized meal.
Method
Twenty healthy individuals, aged 24 to 54, equally divided by sex (body mass index in kg/m^2 18.1-37.7), participated in the study. Blood samples were obtained

twice: after an overnight fast and 2 hours after a meal with different macronutrient composition, in order to assess plasma concentrations of leptin, acylated and des-acylated ghrelin using ELISA kits.
Results
Plasma concentrations of leptin and des-acylated ghrelin were higher in females compared to male subjects. Leptin concentrations were also higher in overweight/obese than in normal weight individuals. No difference has been found between fasting and postprandial concentrations of leptin, acylated and des-acylated ghrelin, nor acylated to des-acylated ghrelin ratio.
Conclusions
No *significant* short-term changes were observed in plasma concentrations of appetite hormones before and after the meal. It seems that the regulation of postprandial satiety is only partially dependent on ghrelin and leptin response. Moreover, these data suggest, that the meal composition (e.g. high proportion of carbohydrates) may affect leptin and ghrelin plasma concentrations to the greater degree than just food ingestion.

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P757

Circulating endocannabinoids are associated with cardiometabolic impairment independently of adiposity in normal weight subjects

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Obesity is characterized by hyperactivated endocannabinoid System (ECS) in brain and periphery and by increased levels of circulating endocannabinoids (cECs), anandamide (AEA) and 2-arachidonoylglycerol (2AG). It is still debated whether in absence of obesity cECs are only modulated by adiposity or if they are associated with cardiometabolic parameters.
We recruited 155 healthy normal weight (NW, BMI: 18.5–24.9 kg/m^2) drug-free volunteers (18–90 years) that, after informed consent, gave fasted blood. Plasma cECs were measured by a validated liquid chromatography–mass spectrometry method.
In females, ($n=94$) AEA ($P=0.014$) and 2AG ($P<0.001$) increased with age; AEA correlated with BMI ($P=0.022$), waist circumference (WC, $P=0.009$), triglycerides ($P<0.001$) and insulin ($P=0.029$), while 2AG correlated with diastolic ($P=0.010$) and systolic ($P=0.001$) blood pressure (DBP and SBP respectively), glucose ($P=0.004$) and triglycerides ($P<0.001$). In males ($n=61$), 2AG correlated with BMI ($P=0.038$), glucose ($P=0.014$), triglycerides ($P<0.001$), insulin ($P=0.028$) and both 2AG ($P=0.008$) and AEA ($P=0.031$) negatively correlated with HDL. After stepwise-multiple regression, triglycerides independently correlated with AEA ($P=0.003$) and 2AG ($P=0.001$) in females and with 2AG in males ($P<0.001$). In females 2AG independently correlated also with SBP ($P=0.016$) and glucose ($P=0.021$), while in males AEA independently correlated with SBP ($P=0.038$) and negatively correlated with HDL ($P=0.047$). Subjects were subdivided in healthy and dysmetabolic (HNW/DNW) subgroups (51/43females, 25/36males) according to the absence or presence of at least one alteration, respectively, among WC (≧88/102 cm, females/males), BP (≧130/85 mmHg), triglycerides (≧150 mg/dl), HDL (<50/40 mg/dl females/males), glucose (≧110 mg/dl). Female DNW had higher BMI, WC, BP, triglycerides (all $P<0.001$) and lower HDL ($P=0.014$) than HNW, also displaying higher AEA ($P=0.005$) and 2AG ($P=0.003$). In males, DNW had higher BP ($P<0.001$) and triglycerides ($P=0.023$) than HNW, but similar cECs. Finally, in NW condition cECs are independently associated with cardiometabolic parameters but not with adiposity parameters, and, particularly in females, can be considered biomarkers of metabolic impairments.

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P758

Irisin plasma concentration in PCOS and healthy subjects is related to body adipose content

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Polycystic ovary syndrome (PCOS) is a common endocrine abnormality connected not only with reproductive problems but also with impaired energy homeostasis leading to metabolic disorders including metabolic syndrome. Irisin (Ir), recently identified novel myokine, has been proposed to mediate some of the positive influence on metabolic disorders. The aim of our study was to search the relationship between Ir plasma concentration in PCOS in the context of metabolic disturbances.
Ir plasma concentration was measured using enzyme immunoassay method in 179 PCOS patients and 122 controls.
Ir plasma level in PCOS patients was 544 ± 767 ng/ml and did not differ from controls (508 ± 522 ng/ml). The concentration of the molecule was significantly higher in obese patients (763 ± 904 ng/ml) than in subjects with proper body weight (488 ± 633 ng/ml, $P=0.002$). In all subjects with high adipose body content (>40%) Ir was significantly higher than in lean persons (<30%) (1004 ± 1003 and 618 ± 782 ng/ml respectively, $P=0.004$). Such observation was recorded also in groups of PCOS patients and controls. No association between Ir plasma level and markers of insulin resistance (WHR, HOMA, fasting plasma insulin level), lipids, neither hormonal status was recorded.
Our findings indicate that Ir plasma concentration is related to adipose body content and confirm that an increased Ir secretion in obesity could result from an adaptive response and irisin-resistance, similarly to the well-known state of leptin-resistance. On the other hand we did not find any relation between Ir and markers of metabolic disturbances. In this respect PCOS patients do not seem to differ from healthy population.

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P759

May the *FTO* gene affect visceral obesity? Study of variant *rs9930506* SNP among the MONW in a Polish population

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Objective
Genetic factors play a major role in obesity. Numerous studies have confirmed associations of the SNP rs9930506 of *FTO* gene with increased BMI, hip circumference and total body weight. The metabolic consequences of obesity depend, to a large degree, on body fat distribution.
MONW individuals (metabolically obese normal-weight), despite their normal BMI, are characterized by visceral obesity and display metabolic properties that may predispose them to developing metabolic syndrome.
Materials and methods
The *FTO rs9930506* SNP was genotyped in 824 young (20 to 40 years of age) subjects, randomly selected from tree different regions of Poland.
We analyzed the influence of rs9930506 of *FTO* gene on the body fat distribution and correlated metabolic parameters in two groups: metabolically obese-normal weight (MONW) and normal weight, classified with consideration to HOMA value (1.69).
All subjects had previously undergone physical examinations, anthropometric measurements (BMI, WHR), densitometry (DXA, dual X-ray absorptiometry) and biochemical measurements (triglycerides, total cholesterol, HDL, LDL, glucose, and insulin).
Results
The prevalence of genotypes of the *FTO* gene was consistent with the Hardy-Weinberg law in the studied group of men ($\chi^2=0.05$, $P=0.8289$) and women ($\chi^2=0.20$, $P=0.6573$). There were no statistical differences in the prevalence of genotypes in MONW and normal weight groups between the two groups. In the group of normal weight men, in homozygous carriers of the risk allele (GG), higher waist circumference was noted ($P=0.0449$). In the group of MONW men, the carriers of the risk allele had increased hip circumference ($P=0.0356$) and C.FAT ($P=0.0350$).
Conclusions
Despite the association of the *FTO rs9930506* SNP with particular parameters in the studied groups, the results did not confirm the impact of this polymorphism on the visceral obesity in MONW individuals. Further studies are required.

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Worsening of cardiovascular risk with increasing number of components of metabolic syndrome in obese non-diabetic individuals

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Introduction
The metabolic syndrome (MetS) is a strong predictor of cardiovascular risk. It is influenced by environmental factors, and its prevalence is high in subjects with obesity.
Design
We assessed differences in glucose- and lipid parameters, and hsCRP and microalbuminuria (MA) in obese subjects with and without metabolic syndrome (MetS) in LifeLines, a population-based study. Included were subjects 18–80 years, with BMI >30 kg/m^2. We excluded subjects known to diabetes, with fasting blood glucose (FBG) >7.0 mmol/l, or using statins. MetS was defined according to revised NCEP ATP III criteria.
Results
A total of 9297 individuals (61% women) participated. Their mean age was 46 $\pm$ 12 years, median BMI 32.3 kg/m^2 (IQR 30.9–34.7). In addition to waist circumference, elevated blood pressure was the most prevalent component (Co) of MetS (60%), while elevated FBG was only present in 21%. There was a gradual and highly significant ($P<0.001$) increase of FBG, HbA1c and serum total and LDL-cholesterol with increasing number of components of MetS (table). We also observed an increase of MA, a marker of endothelial function and cardiovascular risk, but not of hsCRP.

No MetS Co	1	2	3	4+5	*P*
n	1809	3404	2426	1658	
Age-yrs	43 $\pm$ 10	46 $\pm$ 12	47 $\pm$ 12	48 $\pm$ 11	<0.001
FBG mmol/l	4.9 $\pm$ 0.4	5.0 $\pm$ 0.4	5.3 $\pm$ 0.5	5.6 $\pm$ 0.6	<0.001
HbA1c-%	5.5 $\pm$ 0.3	5.6 $\pm$ 0.3	5.7 $\pm$ 0.3	5.8 $\pm$ 0.4	<0.001
Tchol mmol/l	5.0 $\pm$ 0.9	5.2 $\pm$ 1.0	5.3 $\pm$ 1.0	5.5 $\pm$ 1.0	<0.001
HsCRP mg/l	2.6 (1.2–5.6)	2.8 (1.3–5.7)	2.9 (1.4–6.2)	3.0 (1.5–5.6)	0.051
MA mg/l	1.8 (1.1–3.1)	2.1 (1.2–3.9)	2.4 (1.3–5.0)	2.8 (1.5–5.6)	<0.001

Data as mean $\pm$ S.D. or median (IQR)

Conclusion
Both glucose- and lipid-related parameters and albuminuria worsen with increasing number of components of MetS, reflecting the increase of cardiovascular risk associated with this syndrome.

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Health-related quality of life relates to obesity and low-grade inflammation in obese individuals

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Introduction
Obesity is increasingly prevalent in Western society. In addition to medical consequences, obesity also affects health-related quality of life (HR-QOL).
Design
We assessed the differences in HR-QOL in obese participants with and without metabolic syndrome (MetS), by level of obesity and level of inflammation, in the LifeLines Cohort study, a population-based study. In total, 12 765 subjects age 18–80 years, with BMI >30 kg/m^2, participated. Individuals with missing data on HR-QOL, known to have type 1 or type 2 diabetes or who had a fasting blood glucose >7.0 mmol/l were excluded. HR-QOL was assessed using the Short Form-36, and sex-corrected physical (PCS) and mental component score (MCS) were calculated. MetS was defined as having $\geqq 3$ of 5 of the revised NCEP ATP III criteria.
Results
Mean age was 46 $\pm$ 11 years, median BMI 32.4 kg/m^2 (IQR 31.0–34.8), and 44% (60% of males, 35% of females) fulfilled the criteria of MetS. Increasing BMI was associated with a worse score of both PCS and MCS (table). Obese subjects with MetS had lower PCS (49.6 $\pm$ 8.9 vs 51.0 $\pm$ 8.3) and MCS (50.8 $\pm$ 9.3 vs 51.4 $\pm$ 8.8, both $P<0.001$) than those without MetS. Subjects with elevated hsCRP plasma levels had lower PCS than those with normal hsCRP.

		n	PCS	MCS
BMI kg/m^2	30–35	9743	50.9 $\pm$ 8.3	51.2 $\pm$ 8.9
	35–40	2305	49.2 $\pm$ 9.1**	50.9 $\pm$ 9.5
	>40	717	47.1 $\pm$ 9.5**	50.4 $\pm$ 10.4*
hsCRP mg/L	≤ 3.0	4047	51.0 $\pm$ 8.2	51.3 $\pm$ 8.8
	3.0–10.0	2965	49.9 $\pm$ 8.9**	50.7 $\pm$ 9.6*
	>10.0	666	48.9 $\pm$ 9.4**	51.1 $\pm$ 9.5

Data as mean $\pm$ S.D.; hsCRP available in 7678 subjects; *$P<0.05$ and **$P<0.001$.

Conclusion
In obese subjects, MetS is associated with lower HR-QOL. The degree of obesity and low-grade inflammation both are associated with physical functioning rather than with mental health.

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Higher serum levels of the Wnt-signaling antagonist DKK1 in obese respect to Prader–Willi syndrome

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Background
Obesity and in particular visceral adiposity has been related to low bone mineral density (BMD) and greater fracture risk. Subjects with Prader–Willi syndrome (PWS) have lower amount of visceral fat than patients with simple obesity, however can develop osteoporosis. A strong relationship between inhibition of the osteoblast formation and induction of the adipocyte differentiation has been demonstrated. Inhibitors of osteoblastogenesis, such as Dickkopf-1 (DKK1), a Wnt-signaling antagonist, can increase the formation of adipocytes.
Objective and hypotheses
We aimed to analyze the serum levels as well as the expression of DKK1 in obese and in PWS subjects.
Methods
We studied by flow cytometry the expression of DKK1 in peripheral blood cells (PBCs) from 22 obese children (10 M, 9.5 $\pm$ 3.2 years, BMI S.D. 1.9–2.6), 12 PWS adults (4 M, 29.5 $\pm$ 6.4 years, BMI 30.8–65.7 kg/m^2), 6 PWS children (2 M, 8.3 $\pm$ 3.0 years, BMI S.D. 0.82–4.92), as well as 20 controls sex and age matched to obese and PWS children. DKK1 levels were also measured in the sera from patients and controls.
Results
Flow cytometry analysis demonstrated that monocytes, T-lymphocytes and neutrophils from PWS and obese children expressed higher levels of DKK1 respect to controls ($P<0.01$). Interestingly, serum DKK1 concentrations were significantly higher in obese children than in controls ($P<0.01$), but not in PWS patients. Obese children showed an inverse correlation between BMD and abdominal obesity, and PWS adults showed a lower BMD than PWS children.
Conclusions
Our preliminary results highlight the high expression of DKK1 in PBCs from obese and PWS patients, which may have a prominent role in the increased fat depots in both of these subjects. Higher serum levels of DKK1 in obese than PWS subjects could explain the different distribution of adiposity in simply obesity respect to PWS.

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Evaluation of the prevalence of obesity in Minsk city

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Backgrounds
The rapidly increasing epidemic of obesity is one of the most challenging dilemmas facing endocrinologists all over the world today. The scale of the obesity problem has a number of serious consequences for individuals and for government health systems. The aim of our research was the evaluation of obesity and overweight prevalence in Minsk city population within the framework of the Campaign 'Obesity As A Risk Factor of Type 2 Diabetes Mellitus'
Materials
The Campaign 'Obesity As A Risk Factor Of Type 2 Diabetes Mellitus' was an opportunistic screening of individuals applying to the healthcare institutions of Minsk-city during 2 weeks. The evaluation of overweight was estimated on the basis of BMI and abdominal fat mass was assessed by waist circumference, fasting glucose was detected. Distribution by age and sex were taking into account.
Results
Seven thousand and sixty-nine individuals participated in the Campaign, 2564 (25.72%) men and 4505 (63.28%) women. The mean age of the participants was 49.8 + 15.9 years.
According to the obtained data 74.87% (5293) of examined participants had an excess body weight, among them 3490 (65.9%) women, 1803 (34.1%) men. 2380 (33.7) respondents were overweight (65.9% female; 34.1% male); and 2.913(41.2%) respondents were obese (70.9% female; 29.1% male). Normal BMI was registered in 1.776 (25.2%) citizens.The mean BMI made 29.1 + 5.24 kg/m^2. The evaluation of waist circumference revealed that 3285 (76.7%) females had waist circumference above 80 cm and 1122 (45.8%)males – above 94 cm, the mean range of waist circumference in female become 92.1 cm, in male – 92.8 cm. Abdominal adiposity as a predictor of CVD risk and the risk of developing type 2 diabetes was registered in 2638 (61.6%) women and in 581 (23.7%) men.
Conclusions
The results of the Campaign 'Obesity As A Risk Factor Of Type 2 Diabetes Mellitus' revealed the high presence of overweight (33.7%) and obesity (41.2%) in Minsk city population. Abdominal adiposity was registered in 478% respondents (82% women and 18% men).

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Improvement of type 2 diabetes after gastric banding and gastric bypass: medium-term outcomes

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Introduction
Bariatric surgery is associated with improvement and often resolution of type 2 diabetes *mellitus* (T2DM). Our aim was to compare the effects of gastric banding (GB) and gastric bypass (GBP) in glucose homeostasis in obese patients with T2DM.
Methods
From 1995 to 2011, 83 diabetic patients underwent bariatric surgery at our hospital: 37 underwent GB (73% females, mean age 48.3 ± 9.2) and 46 underwent GBP (82.6% females, mean age 49.4 ± 9). We compared prospectively the anthropometric and metabolic parameters and DM resolution until the third year after surgery.
Results
The mean follow-up period was 2.7 years for GB and 1.8 years for GBP. Before surgery, GB patients had a higher BMI than GBP patients (49.3 ± 9.8 vs 45.1 ± 5.3 Kg/m^2). Weight loss in the first, second and third year after surgery was 37.8, 40.4 and 53.3% after GB and 63, 65 and 62.2 after GBP (no significant difference at third year). HOMA-IR improved from 7.8 ± 3.6 to 4.3 ± 3.1, 3.0 ± 1.2 and 2.0 ± 1.1 at first, second and third years after GB and from 7.6 ± 2.5 to 1.6 ± 0.7, 1.7 ± 1.0 and 1.6 ± 0.5 after GBP (no significant difference at third year). HOMA-RI correlated significantly with %EWL at first, second and third years after GB but only at second and third years after GBP. T2DM remission rate was not significantly different between GB and GBP: 56.8% vs 58.7% at first year, 70.6% vs 65.5% at second year and 71.4% vs 55.6% at third year.
Conclusions
Weight loss was slower with GB, but at the third year there weren't significant differences between groups. HOMA-RI improved gradually with GB; in GBP it improved mainly in the first year, as occurred with weight loss. HOMA-RI correlated significantly with %EWL at all times (except at first year for GBP patients), suggesting a weight loss-dependent effect. T2DM remission was not significantly different between groups.

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GLP-1, insulin and glucose levels during mixed test meal before and after gastric bypass surgery in obese patients

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Introduction
Gastric bypass surgery in obese patients results in weight loss, changes in gastrointestinal and pancreatic hormones and improvement of insulin sensitivity.
Methods
GLP-1, insulin and glucose levels were measured after test meal (Fresubin drink a 200 ml; 200 kcal, 15% protein, 30% fat and 55% carbohydrate) before (day 0) and 5, 90 and 180 days after gastric bypass surgery. Glycaemia (mmol/l; glucose oxidase);GLP-1 (Active 7–36) (pM/l; ELISA, ALPCO diagnostics) and insulin (ECLIA, Roche Diagnostics, pmol/l) were determined in 49 obese patients (age: 37.8 ± 1.6; BMI: 43.45 ± 0.77 kg/m^2) in 4 separate days in 0, 15, 30, 45, 60, 90 and 120 min.
Results
There were significant difference between area under the glucose curve (X ± S.D.): 679.12 ± 31.25 mmol/l × min^{-1} (day 0) vs 638.77 ± 29.27 (day 5) vs 658.53 ± 38.64 (day 90) and no difference in day 180 (623.37 ± 28.56). There was significant increase in area under the GLP-1 curve in days 5 (980.12 ± 114.09 pmol/l × min^{-1}), days 90 (682.92 ± 141.39) and days 180 (778.71 ± 210.78) in comparison with day 0 (287.74 ± 118.72) ($P < 0.05$). There was significant difference betwen the area under the insulin curve for days 0 and 5 (33 832.21 ± 3643.67 vs 22 111.59 ± 2399.34) ($P = 0.002$) while there were no differences for day 90 (29 757.06 ± 4135.41) and day 180 (28 378.14 ± 5242.49). There were no significant differences between basal glucose and GLP-1 levels, while there was significant increase in peak GLP-1 levels in day 5 (16.920 ± 2.371), day 90 (14.566 ± 2.914) and day 180 (17.258 ± 3.172) in comparison with day 0 (3.719 ± 1.023) ($P < 0.05$).
Conclusion
GLP-1 response after mixed test meal is significantly increased up to 6 months after gastric bypass surgery. Changes in insulin and glucose levels indicate improvement in insulin sensitivity The improvement in GLP-1 response after test meal after gastric bypass may be responsible for the beneficial metabolic effects of bariatric surgery.

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Vertebral bone marrow fat is increased in obese women: relationship with epicardial fat

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Introduction
Bone marrow fat is considered a risk factor for osteoporosis and fragility fracture. It is not clear if bone marrow adiposity is increased in obesity and how it relates to

other compartments of adipose tissue, in particular visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and epicardial adipose tissue (EAT).
Aim
To evaluate bone marrow adiposity in obese as compared with normal weight women.
Design
Twenty healthy premenopausal women (age 32±8 years, BMI 28±6 kg/m^2, mean±s.d.) underwent body composition evaluation with body impedance assessment, marrow adipose tissue (MAT), and marrow fat unsaturation measurement (L4 level) with proton magnetic resonance spectroscopy (1H-MRS), VAT, SAT (L4 level), and EAT measurement with magnetic resonance imaging, lumbar spine and femoral bone mineral density (BMD) measurement with DXA.
Results
Overweight/obese women ($n=10$, BMI 32±5 kg/m^2) had higher MAT content than normal weight women ($n=10$, BMI 22±1 kg/m^2) (40±9 vs 27±17%, $P<0.05$). MAT correlated with EAT ($r=0.473$, $P<0.05$), age ($r=0.391$, $P<0.05$), BMI ($r=0.410$, $P<0.05$), fat mass ($r=0.440$, $P<0.05$), duration of obesity ($r=0.400$, $P=0.05$), and marrow fat unsaturation ($r=-0.652$, $P<0.001$). In a multiple stepwise regression analysis including MAT as dependent variable and age, BMI, fat mass, duration of obesity, EAT as independent variables, and EAT was the most significant determinant of MAT ($\beta=0.023\pm0.009$, $P<0.05$). Based on medians, women with higher EAT ($n=8$) had higher MAT then women with lower EAT ($n=12$) (41±0.1 vs 28±0.2%, $P<0.05$). Marrow fat unsaturation positively correlated with lumbar spine BMD ($r=0.480$, $P<0.05$).
Conclusion
Bone marrow adiposity is increased and richer in saturated fatty acids in obese premenopausal women and it is related to fat mass and epicardial fat. This seems to confirm an increased risk for osteoporosis in obesity, possibly related to visceral adipose tissue compartments.

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Abstract withdrawn.

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Serum orexin-A levels, insulin resistance and sleep problems in metabolic syndrome

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Background and aims
Orexins are hypothalamic neuropeptides involved in energy homeostasis and sleep regulation. We aimed to find the relation between serum orexin-A levels, glucose, and insulin levels, depression and sleep problems in patients with metabolic syndrome.
Materials and methods
This descriptive, cross-sectional study included 43 patients with metabolic syndrome (patient) and 16 healthy subjects (control, age, and sex matched) who applied to endocrinology outpatient clinic. All participants were assessed with sociodemographic questionnaires, anthropometric measurements (body weight, height, waist, and neck circumference), metabolic parameters, the Pittsburgh Sleep Quality Index (PQ9I), Epworth Sleepiness Scale, and Beck Depression Index.
Results
The mean ages were 40.8±10.1 (23–60 years) and 34.6±9.2 (20–48 years), in patient and control group respectively. There was a significant positive correlation between fasting orexin-A and insulin levels and HOMA-IR ($r=0.371$, $P=0.005$ and $r=0.390$, $P=0.003$ respectively).
The mean serum fasting orexin-A levels were not significantly different (2.06±1.51, 1.21±1.24, $P=0.054$) between two groups. However postprandial orexin-A levels were significantly higher in patients with metabolic syndrome (1.83±1.58, 0.78±0.91, $P=0.007$ respectively) compared to healthy subjects. And fasting Orexin-A levels in females were significantly higher than in male subjects ($P=0.017$).
Global sleep quality was poor (PQ9I>5) in 42.9%, daytime sleepiness scores were high in 58.1% and depression scores were high (>17 points) in 12.8% in the whole group. Global sleep scores were positively correlated with fasting orexin-A levels and waist circumference ($r=0.270$, $P=0.043$ and $r=0.319$, $P=0.037$ respectively). Fasting and postprandial orexin-A levels in subjects who had poor sleep quality were significantly higher compared to subjects with good sleep quality ($P=0.002$ and $P=0.021$ respectively).
Discussion
Higher postprandial orexin A-levels were associated with metabolic syndrome and poor sleep quality. Our findings suggest that orexin A may interact with systems that regulate sleep quality and insulin resistance syndromes and maybe an important therapeutic target for related disorders.

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Relationship of serum TSH with BMI, weight and HOMA-IR in euthyroid obese subjects

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Introduction
Most obese subjects have a normal thyroid function. Despite that, serum TSH seems to be slightly higher in this population, with a positive correlation with the degree of obesity.
Objective
Evaluation of the relationship of serum TSH with BMI, weight, and HOMA-IR in euthyroid obese subjects
Methods
Three hundred obese subjects attending an Obesity Outpatient Clinic and submitted to bariatric surgery between January 2005 and December 2012 were studied by retrospective evaluation of pre-surgical records (weight, BMI, HOMA-IR, TSH, fasting glucose, and insulin levels). One hundred and thirteen subjects were excluded (history of thyroid disease or TSH levels >4.2 mIU/l, $n=45$; insufficient data, $n=50$; other reasons, $n=18$). Results were analyzed using descriptive statistics, Spearman test for correlation analysis and Kruskal-Wallis test for comparison of the parameters between groups; P-value of <0.05 was considered statistically significant.
Results
One hundred and eighty seven subjects were included in the final analyses (151 females and 36 males). Median age of the patients was 44 (min 20, max 67) and median BMI 43.9 kg/m^2 (min 32.0; max. 70.8). Median TSH level was 1.9 mIU/l (min 0.5; max 4.2). There was no correlation between serum TSH and BMI ($r=0.041$; $P=0.577$), weight ($r=0.074$; $P=0.314$) or HOMA-IR ($r=0.060$; $P=0.409$). This lack of association remained when male and female were analyzed separately and when subjects were categorized into quartiles according to BMI, weight, and HOMA-IR.
Conclusion
There was no evidence for an association between serum TSH and BMI, weight, and HOMA-IR in this population of euthyroid obese subjects.

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GLP1 analogs as treatment of postprandial hypoglycemia after gastric bypass for morbid obesity

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Introduction
In a fraction of morbidly obese subjects undergoing gastric bypass (GBP), episodes with late postprandial hypoglycemia (PPHG) develop 1–3 years after

surgery. The pathogenesis of this phenomenon is not fully understood; meal-induced rapid and exaggerated increases of circulating incretins and insulin appear to be partially responsible. Current treatments include low-carbohydrate diets, inhibition of glucose intestinal uptake, reduction of insulin secretion with calcium channel blockers, somatostatin analogs, or diazoxide, a KATP channel opener. Even partial pancreatectomy has been advocated.
In type 2 diabetes, GLP1 analogs have a well-documented effect of stabilizing glucose levels without causing hypoglycemia. Here, we explored GLP1 analogs (exenatide/liraglutide) as open treatment in eight consecutive GBP cases seeking medical attention because of late postprandial hypoglycemic symptoms.
Case reports
Patients were admitted because of hypoglycemia 1–4 years post-GBP surgery. They were thoroughly and negatively investigated for other causes of hypoglycemia than post-GBP hypoglycemia. No glucose modifying drugs were used, and none had diabetes (one patient had remitted preoperative diabetes). Glucose values, measured in connection with a hypoglycemic episode in six of the cases, were 2.7, 2.5, 1.8, 3.5, 2.3, and 1.6? mmol/l respectively.
All eight patients consistently described that the analogs eliminated their symptoms. Furthermore, the symptoms relapsed when, in four of the patients, treatment was reduced/discontinued. In one case, the drug effect was also documented by repeated 24 h continuous glucose measurements.
Conclusion
These open observations suggest that GLP1 analogs might provide a new effective treatment option in patients with problems of late PPHG. The analogs have a more benign side-effect profile than other drugs used against postprandial hypoglycemia, We speculate that their beneficial effect might be by strengthening the counter-regulatory response to hypoglycemia.

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Adipocyte fatty acid binding protein (A-FABP) deficiency promotes diet-induced obesity partially via its regulation on adaptive thermogenesis

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Introduction
Adipocyte fatty acid binding protein (A-FABP) is a fatty acid chaperone that facilitates the efflux of free fatty acid from cytoplasm into circulation. Previous studies show that A-FABP knockout (KO) mice are more susceptible to diet-induced obesity comparing to wild type (WT) littermates. Here we investigate the underlying mechanism of A-FABP in the regulation of diet-induced obesity.
Methods
A-FABP KO mice and their WT littermates were fed on either standard chow (STC) or high fat high cholesterol (HFHC) diet for 24 weeks. Energy expenditure and cold challenge study were performed to evaluate the ability of thermoregulation of mice. Fatty acid transportation rate in adipocytes of WT and A-FABP KO mice was determined by fluorescence and radiation method.
Results
A-FABP expression in BAT and its circulating level are significantly elevated in WT mice in response to HFHC diet induction and acute cold exposure. Oxygen consumption was significantly lower in HFHC diet-induced A-FABP KO mice, and they are cold intolerant while STC-fed A-FABP KO mice show better thermoregulation comparing to their relative WT controls. Basal UCP-1 expression in BAT is significantly higher in A-FABP KO mice when compared to WT mice under STC. However, both HFHC diet- and cold-induced up-regulation of UCP-1 expression are impaired in A-FABP KO mice. The uptake and efflux rate in adipocytes of A-FABP KO mice are significantly lower comparing to their WT controls.
Conclusion
These data suggest that A-FABP is a potential regulator of adaptive thermogenesis, facilitating the FFA transportation from white adipocyte to brown adipocyte for β-oxidation to generate more heat to combat excess weight gain. The up-regulation of basal UCP-1 expression in BAT of A-FABP KO mice may be a compensatory mechanism for maintaining energy homeostasis.

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Offspring of parents with obesity complex investigations: risk of carbohydrate disturbances and diabetes

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Aim of the study
To examine offspring of patients with simple obesity. To ascertain, if there are some disturbances in the carbohydrate or lipid metabolism or unknown type 2 diabetes in these subjects.
Method and subjects
Examined were 132 families, 108 families with obesity, and 24 families without obesity, the control group. Fourteen additional were excluded because of ascertained at the time of examination unknown type 2 diabetes in the parents. In all of the offspring and their parents performed were: weight, height, BMI, WHR HDL, TGD, LDL, and glycaemia HbA1c, in the offspring additional HOMA. The control group included 30 healthy subjects with a negative anamnesis of obesity and/or diabetes in the family.
Results
Observed was overweight and obesity in a high percentage, increased BMI, WHR, significant differences in the level of HDL, TGD, LDL, and HOMA between the examined and control group Additional introduced was HHR< HWRWMI< HJMI< Zot Zot4, and ZL. In seven of the examined offspring ascertained was unknown type 2 diabetes, in 8 morning hyperglycaemia, in 5 glucose intolerance.
Conclusion
i) In offspring of obese parents observed are obesity and disturbances in the carbohydrate, lipid metabolism and unknown diabetes. ii) In offspring of obese patients very important and necessary are repeated prophylactic investigations. iii) Useful will be an education about the prevention of obesity and diabetes. For a better analysis of the obesity is in our opinion important the examination of HHR(height to hip ratio) and HWR(height to waist ratio).

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Downregulation of complement C3 and C3aR expression in subcutaneous adipose tissue in obese Caucasian women

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Background
The central component of the complement system, C3, is associated with obesity, type 2 diabetes and cardiovascular disease however the underlying reasons are unknown. In the present study we evaluated gene expression of C3, the cleavage product C3a and its cognate receptor C3aR in subcutaneous and omental adipose tissue in women.
Methods
Women ($n=140$, 21–69 years, BMI 19.5–79 kg/m^2) were evaluated for anthropometric and blood parameters, and adipose tissue gene expression.
Results
Subjects were separated into groups ($n=33$–36) according to obesity: normal/-overweight ($\leq$30 kg/m^2), obese I ($\leq$45 kg/m^2), obese II ($\leq$51 kg/m^2), and obese III ($\leq$80 kg/m^2). Overall, while omental expression remained unchanged, subcutaneous C3 and C3aR gene expression decreased with increasing adiposity (two-way ANOVA, $P<0.01$), with a concomitant decrease in SC/OM ratio ($P<0.001$). In subcutaneous adipose, both C3 and C3aR expression correlated with apoB, and apoA1 and inversely with waist circumference and blood pressure, while C3aR also correlated with glucose ($P<0.05$–0.0001).
While omental C3aR expression did not correlate with any factor, omental C3 correlated with waist circumference, glucose, and apoB (all $P<0.05$). Further, while plasma C3a/C3adesArg increased and adiponectin decreased with increasing BMI, both correlated (C3a negatively and adiponectin positively) with subcutaneous C3 and C3aR expression ($P<0.05$–0.001) or less.
Conclusions
The obesity-induced down-regulation of complement C3 and C3aR which is specific to subcutaneous adipose tissue, coupled to the strong correlations with multiple anthropometric, plasma and adipokine variables support a potential role for complement in immunometabolism.

Keywords
Complement C3, C3a receptor, C3a/C3adesArg, adipose tissue, body mass index, obesity
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P774

Stimulation of cystatin C production in adipocytes by insulin, GH and triiodothyronine (T3)

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Objective
Cystatin C (CysC) is a marker for estimation of glomerular filtration rate (GFR) and a predictor of mortality, beyond that provided by GFR. CysC increases with abdominal obesity and insulin resistance independently of GFR, not necessarily due to changes in renal clearance but possibly due to changes in production. Non-GFR determinants of CysC remain poorly defined. GH or thyroid hormone excess (acromegaly and hyperthyroidism) lead to concomitant increases in GFR and CysC levels, which can be reversed following successful treatment. We therefore studied whether GH and T3 increase the production of CysC by 3T3-L1 adipocytes *in vitro*.
Methods
3T3-L1 cells were plated and grown for 5d in media containing serum, insulin, and dexamethasone (dex), then kept for 6d in serum-free test media. CysC release was assessed by ELISA and western analysis, responsiveness of the cells to insulin by measuring 14C-2-deoxyglucose (2DG) uptake.
Results
GH (10 nM) stimulated 2DG uptake after 6 h (1.2 ± 0.2-fold) but not after 1 or 4d whereas T3 (10 nM) was stimulatory in longer term (after 4d, 1.4 ± 0.1-fold). Insulin-stimulated 2DG uptake was attenuated by GH (4d) and enhanced by T3 (4d) pre-treatment. 3T3-L1 cells (much more than fibroblasts) express CysC and release the protein into the media where it accumulates in a time-dependent fashion. 10 nM GH- or T3-treated cells released (2.24 ± 0.25 and 2.65 ± 0.32 respectively) more CysC into the media than control-treated cells (1.82 ± 0.22 μg CysC/mg protein x 4d). Among the hormones known and used to enhance adipocyte differentiation, insulin (100 nM, 1.5 ± 0.3-fold) but not dex (100 nM) increased CysC production.
Conclusions
Our data confirm that GH attenuates 2DG uptake stimulation by insulin, and that T3 enhances basal and insulin-induced 2DG uptake in adipocytes. Moreover, insulin, GH, and T3 but not dex enhance the production of CysC by adipocytes *in vitro*, in line with *in vivo* observations.

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P775

Free vs total testosterone as a marker of Leydig cell function and androgen exposure in obese male adolescents

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Background
Data concerning pubertal development and testosterone (T) in obese male adolescents (ObA) are scarce and contrasting. Underperforming T immunoassays and poor assessment of pubertal development might explain discordant findings. Although SHBG is markedly affected, few studies report free T (FT) levels.
Objective
To study if ObA have conserved FT levels despite low total T (TT) and to investigate if FT is a better indicator of androgen exposure than TT by studying pubertal development, testicular volume, and PSA.
Methods
Ninety ObA (mean BMI s.d. $+2.6$), aged 10–19 year at start of a residential obesity treatment program and 90 age-matched (mean BMI s.d. -0.04) controls were studied. Pubertal status was assessed according to the Marshall and Tanner method and testicular volume was measured using a Prader orchidometer. Morning concentration of TT (by LC–MS/MS), FT (by equilibrium dialysis), LH, SHBG, and PSA (by commercial immunoassays) were measured.
Results
Compared to age-matched controls, there was no significant difference in tanner genital staging (obese vs controls:G1:8.8 vs 12.1; G2:18.7 vs 15.4; G3:14.3 vs 13.2; G4:33.0 vs 34.1, G5:25.3 vs 25.3%; NS) and mean testicular volume at the different pubertal stages. While both SHBG (23.3 (17.2–37.1) vs 42.8 (32.9–82.8) nmol/l; $P < 0.001$) and TT (241 (41–339) vs 333 (57.1–502) ng/dl; $P < 0.01$) concentrations were significantly lower in obese boys, FT (5.6 (0.8–8.5) vs 6.3 (0.5–10.6) ng/dl; NS), LH (3.4 (1.7–4.8) vs 2.8 (1.6–4.2) U/l; NS), and PSA (0.19 (0.01–0.38) vs (0.19 (0.01–0.38) μg/l; NS) were comparable. SHBG and TT were lower at all pubertal stages, whereas FT and PSA were preserved except for FT at stage 5.
Conclusion
SHBG and TT but not FT concentrations were lower in ObA compared to lean controls. Since they presented a normal pubertal development, a comparable testicular volume and similar PSA levels, one can state that FT reflects better Leydig cell function than TT in adolescent obesity.

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P776

Application of LC–MS and CE–MS based metabolomics to study type 2 diabetes development in lean, overweight and obese humans

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The risk of type 2 diabetes mellitus (T2DM) development is related to BMI, therefore this disease mainly occurs among overweight (OW) and obese (OB) people. However lean (L) individuals may also suffer from T2DM. The evolution of T2DM is a multistep process and starts with insulin resistance (IR), which may evolve into pre-diabetic state i.e.: impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT). In up to 70% of patients pre-diabetic state evolves into T2DM. In the present study metabolic fingerprinting methodology was used to find metabolites changing with the T2DM evolution. Metabolic differences between healthy, IR and pre-diabetic individuals were evaluated in different BMI groups (L, OW or OB). Study was performed on serum samples obtained from 53 L, 59 OW and 55 OB individuals. Age (mean 50 years) and sex (60% female) were matched between the groups. Samples were analyzed by the two platforms commonly used in metabolomics studies (LC–MS and CE–MS). Health status (control, IR or pre-diabetic) was defined based on fasting glucose level, HOMA-IR, and 2 h 75 g OGTT. Statistical analysis was used to find differences between controls, IR and pre-diabetics in each BMI group. Significant metabolites were identified by analysis of the commercially available standards or MS/MS fragmentation. Branched-chain amino acids were changing with the T2DM evolution independently on BMI. Acylcarnitines discriminated controls from pre-diabetes in each BMI group, however a percentage of change positively correlated with BMI. On the other hand fatty acid amides, cortisol, and sphingosine-1-phoshate were increased in pre-diabetes belonging to L group. The changes in the level of lysophospholipids between healthy and pre-diabetic individuals were higher in L and OW, than in OB. Metabolites changing with T2DM evolution are dependent on BMI.

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P777

The outcome results in patients with type 2 diabetes mellitus and obesity after either adjustable gastric banding (AGB) or Roux-en-Y (RNY) gastric bypass

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The prevalence of the type 2 diabetes and obesity are on the rise globally. Initial interventions for these groups of patients remain diet, exercise and medications. If these measures are insufficient gastrointestinal surgery offers a very good alternative for obesity and type 2 diabetes treatment.

We report the outcome results for patients who underwent either adjustable gastric banding (AGB) or Roux-en-Y (RNY) gastric bypass in the years 2009–2012.
Out of 33 patients (7 men, 26 women, average age 48.4 years), 11 underwent AGB and 22 had RNY. Preoperatively there were no statistically significant differences in: weight, excess of weight, BMI, HbA1c, blood pressure between AGB and RNY subgroups.
In the AGB subgroup the following results were obtained 6 months after the operation: average loss of weight (LOW) 10.87 kg, 18.18% achieved 50% estimated weight loss (EWL), 0% achieved 70% EWL. We observed HbA1c reduction of 5.66 mmol/mol.
Twelve months after the operation average LOW was 14.8 kg, 9.09% achieved 50% EWL, 0% achieved 70% EWL. We observed HbA1c reduction of 7.41 mmol/mol and reduction in BP of 9.6/5.6 mmHg.
In the RNY subgroup 6 months after operation the results were as follows: average LOW 30.9 kg, 71.43% achieved 50% EWL, 23.81% achieved 70% EWL. We observed HbA1c reduction of 24.1 mmol/mol.
Twelve months after the operation average LOW was 39.95 kg, 100% achieved 50% EWL, 58.33% achieved 70% EWL. We observed HbA1c reduction of 13.2 mmol/mol. We observed overall reduction in BP 12.5/4.95 mmHg.
The results show significantly better achievement of EWL and reduction in HbA1c in the RNY subgroup. These results were more sustainable in RNY group 12 months after the operation. Our report supports the more favourable outcomes in patients undergoing RNY gastric bypass procedures.

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P778

Association analysis of the D2 dopamine receptor gene Taq IA polymorphisms in a cohort of Belarus morbidly obese children and adolescents.

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Background
The A1 allele of the DRD2/ANKK1 Taq1A polymorphism (rs1800497) is associated with reduced striatal D2 receptor binding (Thompson *et al.*, 1997; Pohjalainen *et al.*,1998). Associations between Taq1A polymorphism DRD2/ANKK1 gene and reward sensitivity including compulsive overeating were reported (Propper *et al.*, 2008; Davis *et al.*, 2008). To study the association of DRD2/ANKK1 Taq1A polymorphism (rs1800497) with obesity we started genotyping of children and adolescents with morbid obesity (BMI >30 kg/m^2) and normal weight control group children and adolescents. Here we report preliminary results of our investigation.
Population and methods
Seventy obese children and adolescent (4–17 years old) and 164 normal-weight children (4–17 years old) were genotyped using PCR-RFLP analysis of polymorphic alleles rs1800497.
Results
According our preliminary results we didn't find any significant differences DRD2/ANKK1 Taq1A polymorphism (rs1800497) SNP allele and genotypes frequencies between morbidly obese and normal-weight children and adolescents. Please, see the table.
We will continue this investigation in enlarged patient's cohort. The analysis of DRD2/ANKK1 Taq1A genotype of morbidly obese children and adolescents in association with dopamine level and analysis of eating behavior including compulsive overeating will be carried out.

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Table 1 The polymorphic allele and genotype frequency (%) in studied group

		Genotype %		Allele %		
	n	A1A1	A1A2	A2A2	A1	A2
Obese	70	8.6	24.3	67.1	20.7	79.3
Girls	31	9.7	25.8	64.5	22.6	77.4
Boys	39	7.7	23.1	69.2	19.2	80.8
Control	164	7.3	27.4	65.2	21.0	79.0
Girls	104	8.7	26.0	65.4	21.6	78.4
Boys	60	5.0	30.0	65.0	20.0	80.0

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P779

The adaptor protein APPL2 acts as a central regulator of energy metabolism

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Introduction
We have previously demonstrated that APPL1 maintains glucose homeostasis by promoting both actions and secretion of insulin. Although APPL2 is a close homolog of APPL1, the physiological function of APPL2 is vaguely characterized. Thus, we generated a knockout (KO) mouse model in which APPL2 is deleted in pancreatic β-cells and hypothalamus (which is called APPL2 KO mice) to investigate its role in glucose and energy metabolism.
Methods
Male APPL2 KO mice and their wild-type (WT) littermates were fed with standard chow for 12 weeks and then were subjected to acute cold challenge or chronic cold acclimation. A control group under thermoneutral condition was set as well. Basic metabolic parameters related to glucose and energy metabolism were examined.
Results
APPL2 KO mice displayed impairment of insulin secretion compared to its WT controls. Apart from the β-cell phenotypes, APPL2 KO mice displayed increased adiposity accompanied by a dramatic reduction of energy expenditure, despite of similar food intake and locomotor activity. Acute cold challenge experiment revealed that APPL2 KO mice are cold sensitive, which is due to defective lipolytic and thermogenic programs in adipose tissues. Chronic cold acclimation demonstrated that the 'browning' process in subcutaneous white adipose tissue was almost absent in APPL2 KO mice. Such defects were associated with elevated activity of AMPK in hypothalamus.
Conclusion
APPL2 not only modulates β-cell function but also regulates energy metabolism by controlling the hypothalamus-adipose tissue axis.

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P780

Adiposity changes show primacy over the effect of insulin sensitivity changes on androgen profile in obese men integrating short-term weight loss programs

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Introduction
Several studies point towards lower testosterone levels (TL) in patients with obesity and/or insulin resistance (IR).
Aim
To analyze the influence of anthropometric parameters and IR on TL in obese men and weight-dependent changes after a short-term weight loss program.
Methods
Data were collected from a group of male patients, aged 18 to 65, when they attended a first obesity appointment and at reassessment 6 months later. Patients with non-obesity-related hypogonadism or under androgen replacement therapy were excluded. Hypogonadism was considered if TL < 2.6 ng/ml. The anthropometric parameters' impact on TL was controlled for age and IR, as well as the IR impact was controlled for anthropometry and age. Insulin resistance was evaluated by homeostatic model assessment (HOMA-IR).
Results
We analyzed 156 patients characterized by mean age = 41.8 ± 11.7 years, BMI = 45.9 ± 8.6 Kg/m^2, waist circumference (Wc) = 137.1 ± 15.9 cm, TL = 3.2 ± 1.6 ng/ml and HOMA-IR = 6.7 ± 5.8. Hypogonadism was present in 66 (42.3%) males. TL was negatively correlated to age ($r = -0.221$; $P = 0.005$), BMI ($r = -0.344$; $P < 0.001$), Wc ($r = -0.379$; $P < 0.001$) and HOMA-IR ($r = -0.241$; $P = 0.002$). Controlling for age and IR, we observed a negative impact of BMI or Wc on TL ($P < 0.001$, for both). Similarly, controlling for anthropometry and age, a negative impact of HOMA-IR on TL was verified ($P = 0.008$). The 6 months' follow-up appointment was attended by 111 patients. A significant change (Δ) towards decrease on BMI, Wc and IR ($P < 0.001$ for all) and a trend ($P = 0.052$) for TL increase between appointments were observed. An inverse correlation was identified for ΔTL and ΔBMI ($r = -0.325$; $P < 0.001$), for ΔTL and ΔWc ($r = -0.4$; $P < 0.001$) but not for ΔTL and ΔIR.
Conclusion
Hypogonadism is highly prevalent in obese men. Adiposity and IR independently contribute towards decreasing TL. Notwithstanding 6 months was not enough to significantly alter TL, the observed increase was dependent on the decrease verified on adiposity parameters but not on the decrease on IR.

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P781

Hyperleptinemia and insulin resistance in obesity-associated sleep apnoea: Sex-dependent effects of CPAP application

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Obstructive sleep apnoea (OSA) is very common in severe obese patients and has been related to insulin resistance (IR) and hyperleptinemia, and these findings may have effects on food behavior and obesity complications. In order to explore this relationship and the role of sex we have studied 531 patients with morbid obesity (BMI 42.8 + 6.5 kg/m^2). A full polysomnographic study and glucose, insulin and leptin measurements as well as air displacement plethysmography were performed in all of them. Ninety-six obese patients (BMI 45,8 + 7.3 kg/m^2) with OSA were evaluated before and immediately after nocturnal CPAP treatment for 24 h. About 370 out of 531 patients had OSA (AHI 37.7 + 28/h). OSA patients had higher glucose (108 + 29 vs 99 + 26 mg/dl.P < 0.001), insulin plasma levels (20 + 12 vs 16 + 10 (mu/l.P < 0.001) and HOMA index (HOMAi) values (5.5 + 4.1 vs 4 + 2.8.P < 0.001), but lower leptin levels (45.4 + 27 vs 55.5 + 28 ng/ml.P < 0.001) and lower fat mass (48.9 + 7.5 vs 50.5 + 6.6%.P < 0.05) than non-OSA patients. When compared with basal conditions, as a whole group (n = 96) CPAP administration was followed by a reduction in glucose (108.3 + 29.4 vs 115 + 33.7.P < 0.001), and insulin values (21.4 + 16.4 vs 23.8 + 16.3 mU/l.P < 0.01) without any change in leptin concentrations (49.9 + 31.3 vs 50 + 32.3 mU/l. P = NS). Male patients (n = 52) showed reductions in glucose values (109.1 + 22.3 vs 116 + 26.3 mg/dl.P < 0.01) and HOMAi (5.8 + 3.2 vs 7 + 4.9.P < 0.05). However, no changes either in glucose (PreM: 112 + 49.7 vs 114 + 52 mg/dl.P = NS), insulin values or HOMAi (5.1 + 3.9 vs 6.4 + 4.8.P = NS) were seen in PreM women following CPAP. In contrast, postmenopausal women (PostM; n = 21) showed a reduction in glucose (102.9 + 17.8 vs 113 + 28.8 mg/dl.P < 0.01), insulin (18.1 + 11.3 vs 23.5 + 17.5 mU/L.P < 0.05) and HOMAi (4.9 + 4.2 vs 7.1 + 8.1.P < 0.05) with no variation in leptin values (67 + 25.3 vs 65 + 31.9 ng/ml.P = NS) after CPAP. There was no correlation between reduction in apnoea index and decrease in HOMA index after CPAP in any of the subgroups. These data indicate that either OSA in itself or its correction by CPAP has no effects on leptin secretion in patients with morbid obesity. Globally, OSA potentiates IR, but acute correction of OSA by CPAP has more beneficial effects in PostM women and men than in PreM women.

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P782

Use of visceral fat percentage and body fat percentage compared to anthropometric parameters in predicting obesity and cardiovascular risk in Sri Lankan population

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Introduction
Visceral adiposity is shown to be associated with cardiovascular disease. Aim of this study was to evaluate the usefulness of visceral fat percentage (VF%) and body fat percentage (BF%), compared to anthropometric parameters, BMI waist circumference (WC), and waist – hip ratio(WHR) in predicting obesity and cardiovascular risk.
Method
A descriptive cross sectional study conducted within five health divisions in Colombo district in Sri Lanka. Three hundred and eighty two study participants were screened. An interviewer administered questionnaire was used to assess the demographic and medical history. Body fat and visceral fat percentages were estimated using bioelectrical impedance analysis (BIA) method. Cardiovascular risk was calculated using Framingham's cardiovascular risk score.
Results
According to the BMI international cutoff, 3.3% ($n = 4$) males and 13% ($n = 34$) females were obese. Use of Asian Indian cutoff increased this to 36% ($n = 44$) among males and 49.2% ($n = 128$) among females. Based on BF% obesity was 42.6% ($n = 52$) and 83.8% ($n = 218$) among males and females respectively. Central obesity was 39.3% ($n = 48$) and 61.9% ($n = 161$) according to the WC and 37.7% ($n = 46$) and 61.9% ($n = 161$) according to VF% among males and females respectively. VF% showed the strongest correlation with BMI in both females($r = 0.863$, $P < 0.001$) and males ($r = 858$, $P < 0.001$) than with WC (females $r = 0.781$, $P < 0.001$, males $r = 733$, $P < 0.001$) and WHR (females $r = 0.441$, $P < 0.001$, males $r = 0.605$, $P < 0.001$). Ten year cardiovascular risk was > 10% in 37.7% ($n = 46$) males and 25.7% ($n = 67$) females. Cardiovascular risk showed a significant but weak correlation with VF%, and WHR ($r = 0.293$, 0.246, $P < 0.001$) in females but not in males.
Conclusions
BMI is a good predictor of visceral fat mass, compared to other anthropometric parameters like WC and WHR, in both males and females, which are measures of visceral obesity. Cardiovascular risk does not show a strong correlation with anthropometric parameters of obesity.

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P783

Decreased expression of genes encoding thermogenesis-related proteins in adipose tissues of obese patients is not associated with their methylation status

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Introduction
Thermogenesis constitutes an important part of energy expenditure and its disturbances may contribute to the development of obesity. The aim of this study

was to investigate whether the expression of thermogenesis-related genes differs in adipose tissues of obese and normal-weight individuals and if methylation of CpG islands located in the regulatory regions of these genes is involved in this phenomenon.
Materials and methods
The expression of genes encoding β adrenergic receptors (*ADRB1*, *ADRB2, ADRB3*), thyroid hormone receptors α (*THRA*) and β (*THRB*), 5'-iodothyronine deiodinases type 1 and 2 (*DIO1, DIO2*), and of uncoupling proteins (*UCP1*, *UCP2, UCP3*) was analyzed by RT-PCR in visceral (VAT) and in subcutaneous (SAT) adipose tissues of patients with BMI > 40 kg/m^2 and patients with BMI = 20-24.9 kg/m^2. Methylation of the regulatory regions of these genes was studied by real-time PCR preceded by digestion with the methylation-sensitive endonucleases.
Results
The mRNA levels of *ADRB2*, *ADRB3*, *THRA*, *THRB*, *DIO2,* and *UCP2* were significantly lower in adipose tissues of obese than of normal-weight individuals ($P < 0.00001$, $P < 0.00001$, $P = 0.0002$, $P = 0.0001$, $P = 0.0003$, $P = 0.002$ respectively). Obesity was also associated with a lower expression of *ADRB2*, *ADRB3* and *DIO2* in VAT than in SAT ($P = 0.008$, $P = 0.0002$, $P = 0.001$ respectively). The mean methylation of *ADRB2*, *ADRB3*, *THRA*, *THRB*, and *DIO2* in tissues with high and with low expression of a given gene did not differ significantly. In addition, there was no correlation between the level of expression and the degree of methylation.
Conclusions
We observed the decreased expression of thermogenesis-related genes in adipose tissues of obese patients. This phenomenon may result in a lower reactivity of their adipocytes to hormonal and to adrenergic stimuli and in lower potential to activate thermogenesis in response to novel therapeutic compounds targeting proteins encoded by these genes. The regulatory mechanisms involved in this phenomenon remain unknown.
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P784

Different relationship between serum 25OH-vitamin D and expression of vitamin D 25-hydroxylase gene CYP2R1 in subcutaneous adipose tissue of obese and slim subjects.
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Introduction
In Central Europe, vitamin D deficiency is common, and a very pronounced deficiency of this vitamin is observed in obese individuals. We hypothesized that the decreased serum concentration of vitamin D might be in part due to the changed metabolism of this vitamin in adipose tissues.
Methods
We assessed the expression of vitamin D 25-hydroxylase genes *CYP2J2* and *CYP2R1* in adipose tissues of obese and slim patients using RT-PCR. Subcutaneous (SAT) and visceral (VAT) adipose tissues were obtained from obese subjects ($n = 62$, BMI 39-68 kg/m^2) during bariatric surgery (RYGB or VBG) and from non-obese controls ($n = 30$, BMI 20-26 kg/m^2) undergoing scheduled surgical procedures. Serum concentrations of 25OH-vitamin D were measured with the Diagnostics Vitamin D Total Assay (Roche) and IDS manual immunoassay. The results of both tests were correlated with each other.
Results
The mean serum concentration of 25OH-vitamin D was low and similar in obese and slim patients (15.23 ng/ml vs 18.97 ng/ml respectively, $P > 0.05$). The mean expression of *CYP2J2* was similar in VAT (107 ± 20.01 arbitrary units (AU) vs 110 ± 5.63 AU, $P > 0.05$) and in SAT (112.80 ± 8.66 AU vs 107.80 ± 4.64 AU, $P > 0.05$) of obese *vs* slim subjects. Similarly, the mean expression of *CYP2R1* in VAT (120.19 ± 12.43 AU vs 110.05 ± 5.62 AU, $P > 0.05$) and in SAT (119.60 ± 12.60 vs 110.44 ± 5.88 AU, $P > 0.05$) was similar in obese vs slim subjects. A negative correlation ($R = -0.30$) between the expression of *CYP2R1* in SAT of obese individuals and serum concentration of 25OH-vitamin D was found, while it was positive ($R = 0.20$) in SAT of slim patients.
Conclusion
The expression of *CYP2R1* is similar in VAT and SAT of obese and slim patients. Nevertheless, an opposite relationship between serum concentration of 25OH-vitamin D and the expression of this gene in SAT of obese and slim patients has been noted.
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P785

Adiponectin gene expression in subcutaneous and deep neck adipose tissue
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Adipose tissue is an endocrine organ that actively contributes to the development of the metabolic dysfunction but it is not homogenous and the nature of its impact considerably depends on its anatomic location. So far both subcutaneous and deep neck adipose tissue depots were individually related to increased metabolic risk but their particular features were not mutually compared. Adiponectin is an adipocytokine that has consistently showed higher mRNA expression in subcutaneous than in deep or visceral adipose tissue.
The aim of this study was to examine adiponectin gene expression in subcutaneous and deep perivascular neck adipose tissue and their association with metabolic risk factors in patients undergoing neck surgery.
Samples of both subcutaneous and deep adipose tissue along carotid artery were taken in 31 patients during routine thyroid or neck vascular surgery. We analysed adiponectin gene expression in these tissue samples by RQ-PCR method. Serum samples were taken preoperatively to determine insulin, glucose, triglycerides, HDL-cholesterol and C-reactive protein. Anthropometric measurements were also performed. Study participants did not have any inflammatory or malignant diseases.
Adiponectin gene expression was significantly higher in subcutaneous than in deep neck adipose tissue ($P < 0.05$). Statistically significant negative correlations were found between subcutaneous adiponectin gene expression and body weight, waist cifcumference, neck circumference, glucose and HOMA index ($P < 0.05$). Adiponectin gene expression in deep neck adipose tissue was only associated negatively with body weight ($P < 0.05$).
These preliminary results support the hypothesis that subcutaneous and deep neck adipose tissue might have a different secretory profiles. We plan a broader comparative analysis of adipocytokines secretion in these depots of adipose tissue. This study might improve understanding whether these different adipose tissue depots have clinically recognizable endocrine or paracrine role that might be related to adverse metabolic factors or even atherosclerotic changes of carotid arteries.
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P786

Change in cardiovascular risk factors Following bariatric surgery for obesity – First Sri Lankan experience
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Introduction
Obesity is associated with increased prevalence of cardiovascular(CV) risk factors and mortality and the CV risk factors are known to reduce following bariatric surgery. The aim of this analysis was to determine the effect of bariatric surgery on CV risk factors and CV risk score.

Method
A prospective analytical study of the first 15 consecutive patients who underwent laparoscopic Sleeve Gastrectomy procedure from 2009 to 2011 in Colombo. Body weight, systolic (SBP) and diastolic (DBP) blood pressures and lipid profile were recorded preoperatively and at 1 year follow up. CV risk was calculated using Framingham's CV risk score.
Results
Among the studied fifteen patients, 14 were females and one was male. Mean age was 40.07+/−10.93. Preoperative mean BMI was 45.1+/−8.09 and showed a 30.6% reduction ($P<0.001$) after 1 year following surgery. SBP showed a 11.2% reduction ($P<0.01$) and DBP reduction was 14.5% ($P<0.01$). Mean Triglyceride (TG) level showed a 21.1% reduction ($P<0.05$) and HDL cholesterol (HDL-C) level showed a 12.1% rise after 1 year from bariatric surgery. Total Cholesterol and LDL cholesterol levels did not show a significant reduction. CV risk score showed a 17.3% mean reduction at 1 year follow up, which was not statistically significant.
Conclusions
Cardiovascular risk factors, SBP, DBP, TG and HDL-C showed significant improvement following bariatric surgery. CV risk score showed a statistically non significant reduction after 1 year following bariatric surgery.

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P787

The association between metabolic syndrome and android fat mass and android to gynoid fat mass ratio- are Classification and Regression Trees models helpful?

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The aim of the study was to estimate thresholds of android fat mass and android to gynoid fat mass ratio at which metabolic disorders and blood pressure typical of metabolic syndrome appear. Classification and Regression Trees models were used to estimate these thresholds for glucose, HDL cholesterol, triglycerides and systolic and diastolic blood pressure.
Methods
healthy postmenopausal women were recruited for the study. Blood samples were collected for the measurement of plasma concentration of HDL cholesterol, triglycerides and fasting glucose. Blood pressure was measured. Android and gynoid fat mass were assessed using dual energy X-ray absorptiometry.
Results
Metabolic disorders and hypertension in android to gynoid fat ratio groups were more frequent in range from 0,943220 to 1,011458 (glucose from 0,952078, triglycerides 0,965859, HDL cholesterol 1,011458, SBP 0,943220, DBP 0,961549).
Metabolic disorders and hypertension in android fat groups were more frequent in range from 33,25% to 42,15% (glucose from 33,25%, triglycerides 42,15%, HDL cholesterol 35,55%, SBP 34,65%, DBP 34,25%)
Conclusion
Classification and Regression Tress model is applicable to searching for postmenopausal women at risk of metabolic disorders.

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P788

Dietary fat alters the expression of cortistatin and ghrelin systems in the PBMCs of elderly subjects: Putative implications in the postprandial inflammatory response

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Dietary fat influences systemic inflammatory status, which, in turn, determines the progression of age-associated diseases. Peripheral blood mononuclear cells (PBMCs) comprise a subset of white blood cells placed at the crossroad between diet and inflammation, in that they play a key role in the immune/inflammatory system and their gene expression pattern is influenced by diet. Since the somatostatin (SST), cortistatin (CORT) and ghrelin systems have been shown to modulate the inflammatory response, in this study, a nutrigenomic, inflammation-related PBMC-based approach was applied to comprehensively characterize the presence/abundance of the components of the SST/CORT and ghrelin systems in PMBCs, as well as to understand their regulation under diets with different fat composition, and during the postprandial phase in elderly subjects. Our data indicate that the majority of components of the SST/CORT and ghrelin systems are present in the human PBMCs. Particularly, CORT and the SST/CORT receptors (sst2, sst3, sst5 and sst5TMD4), as well as ghrelin, its acylating enzyme (GOAT), In1-ghrelin variant and GHSR1b were detected in PBMCs. Of note, their expression was altered both, in the long-term by diet composition, and in the short-term, during the postprandial phase, suggesting a potential relevant role of these systems in regulating PBMCs response to nutrient intake. Of particular relevance is the postprandial elevation of the expression of CORT, sst2 and sst5 in PBMCs of subjects under an n-3 PUFAs-enriched diet, which could help to explain the positive effects of this diet in reducing the inflammatory response.

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P789

Climate and risk of obesity: di@bet.es study

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Introduction
It has been suggested that the lack of exposure to low ambient temperatures may be a contributor to the development of obesity. The aim of this study was to study possible associations between climate and the risk for obesity in the Spanish population using an ecological focus.
Methods
The Di@bet.es Study is a national epidemiological study designed to determine the prevalence of diabetes, obesity and other cardiovascular risk factors in Spain. The overall sample comprised 5061 persons in 100 clusters (health centres or their equivalents). The participation was 57%, and data were gathered the following: clinical and demographic characteristics and lifestyle survey, physical examination and oral-glucose tolerance test. Basic climate data collected were mean annual temperature (°C), mean annual precipitation (mm), mean relative humidity (%), mean annual number of hours of sunshine (hours), and altitude (metres) for each study site according to data from the Spanish National Meteorology Agency (1971–2000).
Results
The prevalence of obesity in the different geographical areas divided according to mean annual temperature quartiles were 26.9% in quartile 1 (mean annual temperature 10.4–14.5°), 30.5% in quartile 2 (mean annual temperature 14.5–15.5°), 32% in quartile 3 (mean annual temperature 15.5–17.8°), and 33.6% in quartile 4 (mean annual temperature 17.8–21.3°) ($P=0.003$). Logistic regression models adjusted for multiple sociodemographic variables (age, gender,

population type, educational level, work status, marital status) and lifestyle (physical activity, Mediterranean diet score, smoking), showed that, as compared with quartile 1, the odd ratios for obesity were 1.22 (1.02–1.45) in quartile 2, 1.34 (1.12–1.61) in quartile 3, and 1.37 (1.13–1.65) in quartile 4 ($P=0.004$ for difference, $P<0.001$ for trend).
Conclusion
Our study reports an association between ambient temperature and the risk of obesity in the Spanish population. Further research is needed to confirm our findings and to expand knowledge in this field.

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P790

Sex hormone binding globulin, total and HMW adiponectin and insulin resistance among normal weight postmenopausal women with metabolic syndrome

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Visceral obesity among postmenopausal women often leads to the development of metabolic syndrome (MS), but there is a subgroup of normal weight postmenopausal women displaying metabolic disturbances who are diagnosed to have MS. These subjects often show insulin resistance, however little is known about the effects of adiponectin and sex hormone binding globuline SHBG) on MS in this subset of women.
The aim of the study was
i) to assess serum SHBG, total and HMW adiponectin, and HOMA-I in normal weight postmenopausal women with MS, ii) to compare them with concentrations in normal weight postmenopausal women with healthy metabolic profile, iii) to investigate relationships between adiponectin, insulin resistance and SHBG in normal weight women after menopause.
Methods
Metabolic profile, waist circumference and blood pressure were analyzed in ninety four postmenopausal women with BMI < 25 kg/m^2, aged 53–65. Subjects were classified as:
1. metabolically healthy (having 0 or 1 metabolic abnormalities) - 48 women,
2. having 2 metabolic abnormalities (29 women),
3. subgroup with metabolic syndrome, according AHA/NHLBI definition (≥ 3 abnormalities) - 17 women.
Estimation of serum fasting insulin, SHBG, total and HMW adiponectin were done using commercial radioimmunoassay kits and HOMA-I was calculated.
Results
There were no statistically significant differences between groups in age and BMI, however waist circumferences were higher in the MS subgroup when compared with metabolically healthy subgroup. SHBG ($P<0.05$), total adiponectin ($P<0.01$) and HMW adiponectin ($P<0.05$) were lower and HOMA-I ($P<0.05$) was significantly higher in women with MS when comparing with metabolically healthy subgroup. When analysis was performed for all women, low SHBG concentrations were associated with an elevated HOMA-IR ($P<0.01$) and waist circumferences ($P<0.01$). Total and HMW adiponectin levels also correlated inversely with HOMA-I ($P<0.01$). SHBG was significantly and positively linked with both total and HMW adiponectin ($P<0.01$).
Conclusion
In normal weight postmenopausal women low SHBG, total and HMW adiponectin concentrations are connected with insulin resistance and may be predictors of the development of metabolic syndrome.

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P791

Childhood obesity alters innate T cell frequency and function resulting in loss of regulation and increased inflammation

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Background
Childhood obesity now represents a major public health concern. Being obese in childhood appears to increase the risk of severe obesity in adulthood. Obesity is associated with co-morbid conditions such as type 2 diabetes and cardiovascular disease. Underpinning obesity is a state of chronic sterile inflammation. Recently the invariant natural killer T (iNKT) cell, an innate T cell was shown to act as a metabolic regulator and altered by obesity both in adults and children.
Hypothesis
We hypothesised that other innate T cells populations (Mucosal associated invariant T (MAIT) cells and Vδ3 T cells are impacted by obesity in children resulting in loss of regulation and increased inflammation.
Methods
We investigated the frequency and function of MAIT and Vδ3 T cells in a cohort of obese children (mean age 12.8, mean BMI *z*-score 4) and compared to a non-obese cohort of children (mean age 12.4, mean BMI *z*-score 0.3) by multi-colour flow cytometry. We correlated immune parameters with BMI, insulin levels and age using graph pad prism.
Results
We show that in obese children MAIT cells are increased in frequency (4% vs 1.8%) and a greater proportion produce IL-17 (10% vs 2%) when compared to non-obese cohort. Furthermore, MAIT cells upregulated PD-1 expression a marker of late activation/exhaustion. Vδ3 T cells were reduced in frequency (0.7% vs 1.1%) in obese children and upon stimulation a greater proportion produced high levels of the regulatory cytokine IL-10 compared to non-obese cohort (20% vs 1%).
Conclusion/Interpretation
Immune dysregulation leads to increased inflammation. We show that MAIT cells; a population of immmunoregulatory cells are expanded in childhood obesity. These cells display an altered/exhausted phenotype with increased IL-17 production; a cytokine implicated in the pathogenesis of numerous diseases including cancer and autoimmunity. In contrast, Vδ3 T cells are depleted in obese children and produce increased levels of IL-10, suggesting a possible compensatory mechanism to the observed systemic inflammation. Collectively this data shows significant immune dysregulation in obese children.

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P792

Metabolic and hypertension control in diabetic patients submitted to bariatric surgery

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Background
Type 2 diabetes and Hipertension are common in obese patients. Bariatric surgery is effective in sustained weight loss, but also improves glycemic and hypertension control. A high percentage of diabetes remission occurs.
Methods
Retrospective study of type 2 diabetic patients submitted to bariatric surgery between 2006 and 2013 in a central hospital. Primary endpoint was evaluation of diabetes and hypertension remission, 2 years after surgery. It was also measured weight changes, BMI, blood pressure, glycemic control before and after surgery. We used descriptive statistics, student t-test and chi-square distribution.
Results
A total of 150 bariatric procedures were done. Laparoscopic adjustable gastric banding (LAGB) was the most common procedure (47%), followed by sleeve gastrectomy (37%) and gastric bypass (16%). The mean age of patients was 48.2 ($\pm$9.7) years old, with a predominance of women (87%). In the LAGB group there was a BMI reduction from 48.9 to 40.8 kg/m^2, in the sleeve group from 44.9 to 32.9 kg/m^2 and in bypass from 46.9 to 35.5 kg/m^2. There was an improvement in glycemic control in all techniques, but it was most important in the bypass group, with a remission rate of 72.2% (vs 52.7% of sleeve and 36.9% in LAGB; $P=0.024$). The prevalence of hypertension was lower in the bypass group (54%) than in sleeve group (75%). In terms of hypertension control, there was a reduction in the number of classes prescribed in the three groups, with the best remission rate also seen in the bypass group (69.2%).
Discussion
There was an important remission rate of diabetes and hypertension after bariatric surgery, mostly in the gastric bypass group, where weight loss was also larger and the patients younger. The remission rate seems to be related not only with weight loss, but also with metabolic changes linked with each type of procedure.

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Paediatric endocrinology

P793

Effectiveness of GH therapy in children with normal results of GH stimulation tests and with partial GH deficiency is similar and depends on the severity of IGF1I deficiency

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Introduction
GH therapy in children with normal GH peak in stimulation tests (GHST) is still a matter of discussion. Recently, GH deficiency (GHD) has been defined as secondary IGF1 deficiency (IGFD), however GHST still remain the main procedure in diagnosing GHD.
The aim of present study was to compare GH therapy effectiveness in the patients with normal results of GHST (normGH) and with isolated partial GHD (pGHD), with respect to IGF-I secretion before treatment.
Patients and methods
Analysis comprised 75 patients (56 boys), age 12.1±2.9 years (mean±S.D.) with short stature, GH peak in GHST >10 ng/ml and excluded primary IGFD by IGF1 generation test (normGH group), compared with 182 patients (142 boys), age 12.3±2.7 years, with GH peak in GHST 5–10 ng/ml (pGHD group). In each patient IGF-I concentration before treatment was assessed. The patients with normGH and with pGHD were qualified according to IGF1 S.D. for age and sex into the following subgroups:
i) normGH1 and pGHD1 – IGF1 SDS <−2.0 (severe IGFD);
ii) normGH2 and pGHD2 – IGF1 SDS between −2.0 and −1.0 (partial IGFD);
iii) normGH3 and pGHD3 – IGF1 SDS >−1.0 (no IGFD).
All the patients were treated with GH during 4.9±2.6 years, up to final height (FH). In each patient FH SDS increase with respect to height SDS before treatment (ΔHSDS) was calculated.
Results
The best ΔHSDS was in normGH1 (1.86±0.93) and pGHD1 (1.65±0.89), the worse in normGH3 (0.99±0.71). Similar ΔHSDS was observed in normGH2 (1.44±0.77), pGHD2 (1.29±0.77) and pGHD3 (1.44±0.92). There was no significant difference in ΔHSDS between normGH1 and pGHD1 ($P=0.42$), between normGH2 and pGHD2 ($P=0.49$), and between normGH3 and pGHD3 ($P=0.10$).
Conclusion
The effectiveness of GH therapy was better in the patients with decreased IGF-I secretion before treatment, being the highest in severe IGFD and almost independent from the results of GHST.

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P794

Inflammation: a risk factor or a consequence of metabolic diseases in obese prepubertal Iraqi children

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Background
Childhood obesity is a condition where excess body fat negatively affects a child's health or wellbeing. Potential risk factors for cardiovascular diseases (CVD) tend to cluster in childhood and are strongly associated with obesity.
High levels of free fatty acids originating from visceral fat reach the liver through the portal circulation and stimulate synthesis of the triglyceride-rich lipoprotein VLDL the resulting elevation in VLDL can lower HDL cholesterol.Adipose tissue can also synthesize cytokines such as IL-6. Leptin is a hormone produced by the adipocytes to regulate food intake, its circulating levels directly correlate with the amount of body fat and BMI.
Previous researchers had provided evidence suggesting that *ob* gene expression is up regulated by some inflammatory cytokines such as IL-6.
Aim
The aim of this study is to explore the accumulative effect of serum leptin, interluikin-6, cholesterol and HDL in order to detect the presence of any impairment of these parameters as risk factors for metabolic cardiovascular syndrome in obese prepubertal children, in an attempt to overcome the increased health risk associated with obesity in children.
Subjects and methods
Eighty prepubertal children age range between (5 – 11) years old were enrolled in this study. Divided according to their weight into two groups:
i) Obese group 50 subjects, Lean group 30 aged matched subjects.
ii) Circulating serum leptin, IL-6, cholesterol and HDL were measured.
Results
Serum leptin IL-6 and cholesterol showed a significantly higher values in obese children than in leans. No significant correlations were found to exist between leptin and IL-6 in both groups. However a significant correlation was found between cholesterol and IL-6 in obese children.
Conclusion
IL-6 was elevated metabolically so inflammation might be a risk factor rather than a consequence of cardiovascular metabolic syndrome in obese children. In the light of these findings interventional measures are necessary in order to prevent excessive weight gain during childhood.

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P795

A case of velocardiofacial syndrome with short stature associated with partial GH deficiency

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Introduction
Velocardiofacial syndrome (VCFS) also known as DiGeorge or chonotruncal anomaly face syndrome, is a rare genetic disease caused by a microdeletion in the long arm of chromosome 22, having a prevalence of approximately 1:7000 to 1:4000. VCFS has a wide spectrum of more than 200 physical manifestations including: cleft palate, heart and facial abnormalities, eye pathology, problems with feeding, including nasal regurgitation, middle-ear infections (otitis media), low calcium due to hypoparathyroidism, short stature.
Case report
We present a 9 year old boy born from unrelated parents, referred to the Clinic of Endocrinology for his short stature. On clinical examination his height was of 114 cm (−3 S.D.), and his weight was of 16.5 kg (−4.3 S.D.). Dimorphic features included: elongated face, almond shaped eyes; malar flatness; normally formed but protuberant ears with attached lobes, low-set ears, mild micrognathia. The suspicion of VCFS was revealed and a blood sample was taken in order to prove 22q11 microdeletion. Hormonal investigations showed euthyroid status, low normal IGF1 level and low basal GH, with subnormal answers by clonidine and arginin tests (peak GH was beneath 10 ng/ml). These data and delayed bone age (3 years), represented arguments for initiating therapy with recombinant GH. We found other modifications related to the VCFS.Heart ultrasound revealed stage III mitral insufficiency with anterior mitral valve prolapse, aortic bicuspidy with stage I aortic insuffiiciency, ascendent aortic dilatation.
Discussions
Short stature is a frequent finding in VCFS and has been reported to occur in 36 to 67% of these patients, postulated to be due to intrauterine growth retardation, feeding difficulties and congenital heart defects. The incidence of GH deficiency in this particular genetic context is not known.

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P796

Kearn-Sayre syndrome associated with adenohypophysis agenesis: long term follow-up

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Kearns-Sayre syndrome (KSS) is a mitochondrial disorder characterized by progressive external ophthalmoplegia, pigmentary retinopathy, together with cardiac conduction defects, muscle abnormalities and endocrinopathies such as growth hormone deficiency (GHD), diabetes and hypoparathyroidism.
We present a 2 years 9 months-old boy with clinical and biochemical diagnosis of KSS and GHD. He was referred with failure-to-thrive. He was born at term from healthy 2 cousins, parents. Postnatal he was followed in intensive care and he had tracheotomy for 1.5 years. On admission, weight was 11.6 kg (3-10 p), height was 85 cm (<3 p), bilateral ptosis and scar on the tracheal notch. Biochemical analysis was normal except mild anemia. Hormonal investigations revealed central hypothyroidism (TSH: 1.72 mIu/ml, sT4:0.66 ng/dl (0.67-1.2). L-thyroxin treatment was started. Thyroid USG showed hypoplastic gland (1.23 ml).
GHD was determined (stimulated GH:1.81 ng/ml). IGF1 was 17.87 ng/ml (24-152), IGFBP-3 was 633 ng/ml (232-6595). Small sella, thin infundibulum and agenesis of adenohypophysis were shown in MRI. GH was started.
Cardiac examination was normal. Retinal examination revealed venous dilatation and an increase in vascular tortuosity. Lipid deposition was found in muscle biopsy.
Homozygous missense mutations were found in Mt-DNA rRNA RNR1 (1438 A>G) and RNR2 (1766 T>G and 3010 G>A). Additionally homozygous missense mutation was determined in Mt-DNA 8860 A>G.
KSS was confirmed and Coenzyme Q and riboflavin was started.
At the last visit he was 5 years 9 months old, height was 121.5 cm (90 p) and weight was 23 kg (90 p). Excellent result has been achieved with GH therapy in our patient.
Conclusion
GHD caused by adenohypophysis agenesis in the present case and this association has never being reported up to now.

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A new cause of liver cirrohosis in childhood: Long-term uncontrolled obesity

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NAFLD has become the most common cause of chronic liver disease in obese children.
Two years-one month-old boy admitted to clinic for obesity. Parents were first cousin. Weight was 20 kg (>90p), height was 84 cm (50 p), BMI was 28.34 kg/m^2 (>97 p). Physical examination was normal except diffuse hypertrichosis and right kriptoorchidism. On the follow-up, he never lost weight. At 4-years-old, FPG was 112 mg/dl, AST was 67 IU, ALT was 72 IU; and OGTT performed and hyperinsulinism was determined. USG revealed hepatomegaly. Metformin therapy was recommended but parents never used it and patient was not admitted to hospital until the age of 10 years 8 months old. At that age hypothyroidism was diagnosed and L-thyroxin was started. At 11-years old, hypertension appeared and Blount disease was diagnosed. Glaucoma was determined. Cushing syndrome excluded by overnight-dexamethasone-test. OGTT performed 2nd time and IGT was found. Metformin started. He had operation for kriptoorchidism. Parents never took him to hospital until the age of 15 At 15 years-old, BMI was 43.5 kg/m^2, type 2 diabetes (FPG was 216 mg/dl, HbA1c 10.9%) and secondary hemophagocytosis was diagnosed. Hypertension and cardiac hypertrophy was determined. USG revealed grade 2 hepatosteatosis in addition, coarse and granular echo pattern. On the MRI, vertical line of liver diminished, left lobe was hypertrophic, diminishing and small nodulation was found in right lobe of liver. Dilatation of portal venous system, expanded umbilical vein, and splenomegaly were also determined on MRI and chronic liver disease was diagnosed. Liver biopsy revealed cirrhotic nodules and inflammatory cell invasion. At 15- years-9 months-old, he had hematemesis and encephalopathy. Ammoniac was 599 μg/dl. Endoscopic examination showed varicose vein just the lower esophageal sphincter.
Liver cirrhosis due to NAFLD caused by obesity in the present case and this association is rare in childhood.

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Delayed puberty in a girl with ataxia telangiectasia: Multiple endocrine dysfunctions

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Introduction
Ataxia telangiectsia (AT) is a rare, genetic, primary immune deficiency disease characterized by immunodeficiency and neurological manifestations, with predisposition for infections, cancers, and autoimmune diseases. This case illustrates the affection of endocrine system in the form of hypothyroidism and hyper-gonadotrophic hypogonadism.
Case Report
A 14-year-old girl presented to our clinics at Hamad General Hospital, with history of progressively increasing difficulty in walking and hand movements since age of 8 years. She was prepubertal (Tanner 1 breast development), underweight (BMI S.D. = −2.5) with normal stature (Ht S.D. = 1.1). She had an expressionless face, conjunctival telangiectasia, dysarthria, diminished reflexes, dystonina, and ataxic gait. CBC revealed lymphopenia (between 1000-1400 cells/ul) and α-fetoprotein (246 IU/ml). Liver and renal function tests were normal. Serum IgG = 2940 mg/dl, IgA <6.6 mg/dl, and IgM = 135 mg/dl. Serum IgG subclasses levels and anti-vaccine titers were normal. Lymphocyte subsets showed slightly low CD3, CD4, and CD19. Free thyroxine was low (7.8 pmol/l), TSH was high (>100 mIU/l), and anti-thyroid perioxidase titer high (>1000 U). Serum insulin-like growth factor1 (IGF1) and morning serum cortisol were normal. Trans-abdominal pelvic ultrasound demonstrated small hypoplastic uterus and rudimentary ovaries, and cranial MRI showed marked cerebellar and vermis atrophy with iron deposition in the pituitary.
Discussion
Occurrence of primary hypothyroidism and hypergonadotrophic hypogonadism points out to an autoimmune aggression in cases of AT to thyroid and ovaries. Conclusion: In patients with AT endocrine manifestations may include hypothyroidism and hypogonadism and should be kept in mind when evaluating delayed puberty in this condition.

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P799

Vitamin D assessment in infants with prolonged hospitalisation

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Background
Vitamin D deficiency – a common condition in infants without supplementation – leads to a variety of health impairments.
Objectives
To assess 25-OH-vitamin D (VD) status in infants with prolonged hospitalisation, without direct exposure to sunlight.
Materials and methods
Twenty-two infants (mean age 6 years 3 months), admitted into Recuperation Department of a Children Hospital for nutritional rehabilitation, were enrolled. Infants were formula milk fed (48 UI/100 ml) and vitamin D supplemented with 1000 UI/day (D3 oil). Babies' mothers have not been monitored and didn't take any vitamin D supplements during pregnancies. Infants were clinically evaluated and haematological and biochemical profiles were performed. VD concentrations (automated chemiluminiscent method) were measured 40 days after admission (mean period). Statistics was performed with SPSS 17.0. The study was approved by the Local Ethical Committee.
Results
VD levels were 27.35 ± 11.30 ng/ml (mean ± S.D.). Despite supplementation with recommended doses of D3, 65.6% of infants were VD insufficient (20-30 ng/ml) and 22.9% VD deficient (<20 ng/ml), only 3 babies had targeted VD level over 30 ng/ml. Calcium levels were in the reference ranges. 85.7% of infants had anemia (haemoglobin values <13 g/dl), and 28.6% had iron under the cut-off value for iron deficiency anemia (<8 ng/ml). We cannot establish any correlation

between VD levels and haematological parameters. A slightly negative correlation ($r = -0.4$) was found between VD and BMI. None of the babies presented clinical evidence of rickets, but rickets may occur after a period of an improper circulating VD level.
Conclusion
Monitoring the status of VD in infants with prolonged hospitalisation and supplementation with adequate doses of D3 should be of concern for paediatricians, to ensure a favourable development of those children.

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P800

Small for gestational age (SGA) children: Results after 3 years of GH therapy

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Introduction
GH therapy (rhGH) improves growth outcome in children born small for gestational age (SGA). Growth velocity is maximum in the first year of therapy. Early diagnosis and treatment optimizes the final height.
Objectives
Evaluation of efficacy and safety profile in the first 3 years of rhGH treatment in ten SGA children.
Methods
The study enrolled ten SGA children (6 boys, 4 girls). All patients were given a mean dose of 0.034 mg/kg/d and followed for a period of minimum 3 years (mean 4.32 years).
Results
The mean height expressed in standards deviations (S.D.) raised from −2.43 at diagnosis to −0.68 after 3 years (Table 1); this achievement declined in time.
In the first 3 years of therapy there were no cases of diabetes mellitus or impaired glucose tolerance (>140<200 mg/dl), one patient (10%) presented impaired fasting glucose (>100<126 mg/dl), one patient (10%) developed hypothyroidism and four patients (40%) presented subclinical hypothyroidism treated with L-thyroxin. No malignancies were observed to date.

Table 1 Data from the first 3 years of rhGH therapy

Parameter	Baseline	1yr	2ys	3ys
Chronological age (years)	6.29	7.29	8.29	9.29
Bone age (years)	4.05	4.75	5.56	7.15
Mean IGF1 values (ng/ml and S.D.)	77.5 (+0.24)	305.38 (+1.49)	258.71 (+1.54)	329.85 (+1.26)
Height (S.D.)	−2.43	−1.37	−0.91	−0.68
Growth velocity (cm/month)	–	0.98	0.77	0.6
Weight (S.D.)	−2.3	−0.9	−0.3	−0.52

Conclusions
Growth hormone therapy significantly improves growth in children born SGA, with a favorable safety profile. Maximum height velocity was registered in the first year of treatment, 11.76 cm/year; in the second and third year height velocity declined to 9.24 cm/year and 7.2 cm/year respectively. There were no severe side effects.

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P801

The longitudinal study of replacement therapy of secondary hypothyroidism in newborn with brain damage

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Introduction
Secondary hypothyroidism is observed in children after brain damage. The aim of the study is evaluation of mental development in preterm-born children during replacement therapy with l-thyroxin because the secondary hypothyroidism.
Description of methods
The motor and mental development preterm new-borns with secondary hypothyroidism treated with l-thyroxin since the second week of life were compared with the development of preterm new-born with secondary hypothyroidism treated since the 4th week or later. The motor development was evaluated, and the mental development and IQ was assessed in the Wechsler Intelligence Scale for Children in the seventh and tenth year of life.
Results
Earlier achievement of the milestones of motor development, i.e. sitting, standing, and walking was observed in children from group who received early treatment with modest doses of l-thyroxin. In this group, all infants acquired the motor functions statistically significantly earlier in comparison to the infants from group with delayed treatment. In the 7th year of life, the IQs were significantly higher in group I treated since the second week of life in comparison to group II.

The mean IQ according the wechsler scale for children revised (WISC-R)	**I Group IQ**	**II Group IQ**	***P***
7-th year of life	102.6±20.1	82.3±21.3	0.003
10th year of life	104.8±22.3	80.5±20.8	0.001

Statistic significant, $P<0.01$.

Conclusions
The early replacement therapy with l-thyroxin initiated in the 2nd week of life may improve long-term mental development in children.

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P802

Causes of short stature in endocrinology: about 800 cases

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Introduction
The causes of short stature are various and their frequency depends on whether we consult in pediatric or endocrinology.
Although endocrine pathology is involved in a little <10% of cases, its recognition is important because it leads to a specific treatment that enhances the stature prognosis.
Aim
Search etiologies statural delays observed in endocrinology and assess the frequency of GH deficiency.
Population methodology
800 patients were followed at two departments of endocrinology in 13 years. All patients underwent a complete clinical examination specifying auxological characteristics and a systematic review (overall balance, FT_4, TSH, IGF1, and bone age). The explorations were completed according to the context.
Results
The etiologies of delay stature are following: constitutional 28% delay puberty, 17% familial, 22.65% visceral, and inflammatory disorders 34%, endocrine abnormalities 16.20, small gestatinal 3.03%, chromosomal disorders 1.87%, constitutional bone diseases 1.15%, steroid therapy 0.14%, and underfeeding 0.14% growth insufficiency represented 13.27% of the causes of delay stature. primary hypothyroidism and hypoparathyroidism represent 3.17 and 0.28% of cases.
Discussions and conclusion
3/4 of delay stature are not related to endocrine etiology. Constitutional and familial short tall associated or not with delayed puberty represent more than half of etiologies.
20% of cases are related to visceral affections dominated by digestive malabsorption (Giardiasis and celiac disease).
The low proportion of hypothyroidism in our series (3.17%) is reassuring, knowing that neonatal screening is nonexistent. systematic realization of karyotype in front of a small girl is difficult in our country. Of this fact the proportion of Turner syndrome is unknown and certainly underestimated.

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P803

Characteristics of nutritional status in children with alimentary obesity

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Objective
To study feeding habits in children of different ages with alimentary obesity compared with normative values.
Methods
We compared 3 days food diaries of 98 children with alimentary obesity observed in the Endocrinology Department of University Hospital (Minsk) with nutritional standards of healthy children recommended by Belarusian National Center for Hygiene, Epidemiology and Public Health – control (K). Patients were divided into three age groups: 1st 5–6 years (6.1 ± 0 years; BMI 25 ± 4.2 kg/m^2) – ten peoples (10.2%); 2nd 7–12 years (9.7 ± 1.1 years; BMI 27 ± 4.4 kg/m^2) – 42 peoples (42.8%); 3rd 13–17 years (14.7 ± 1.9 years; BMI 32.3 ± 5.2 kg/m^2) – 46 peoples (47%). The frequency of different food groups, main meals, snacks consumption were studied with the assessment in points (p) 0p – a child didn't eat products of this group, 1p eat every day, 2p eat one to two times a day, 3p eat three or more times a day. Results were processed using SPSS 18.0.
Results
Obese children showed a significant decrease in consumption of porridges and pasta (P (three groups) = 0.0001), starchy vegetables (p2-K = 0.046), and (p3-K = 0.014); fruits (p2-K = 0.046), dairy products (p1-K = 0.046), (p2-K = 0.006), (p3-K = 0.005); with increasing - sweet beverages and juices (p1-K = 0.037) and (p2-K = 0.007), oils and fats (p1-K = 0.01), (p2-K = 0.004). The frequency of snack consumption were less in children with obesity vs the standard ratios (group 1, 2.10 ± 0.57, group 2, 1.57 ± 0.1p; and group 3, 1.26 ± 0.80p, norm 3) (p1-K = 0.022, p2-K = 0.001, and p3-K = 0.0001).
Conclusions
The reduced consumption of cereals, pasta, starchy vegetables, fruits, dairy products, oils, reducing the frequency of snacking; increased - sugary drinks and juices, oils, and fat contributes to the development of obesity in children.

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P804

Perinatal risk factors of the development of obesity in children

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Aim
To identify perinatal risk factors of the development of simple obesity in adolescence.
Methods
We analysed retrospectively 327 histories of development in pubertal children, with the division into two groups: group 1 – 158 obese children (age 14.6 ± 2 years, BMI 33.4 ± 5 kg/m^2), group 2 – 169 normal-weight patients (age 12.6 ± 2.2 (P = 0.2); BMI 20.5 ± 1.2 kg/m^2 (P < 0.05)) from the University Hospital (Minsk). We collected anamnesis clarifying gestational age, account and complications of pregnancy, and delivery, presence/absence of chronic intrauterine hypoxia, family obesity, parental smoking; estimated body weight (high-birth-weight and small to gestational age children were excluded from the study), and growth at birth. The results were processed using SPSS 18.0.
Results
In group of obese children birth weight was 3.6 ± 0.45 kg, height 52.1 ± 2.9 cm, gestational age 37.3 ± 8 weeks, control 3.35 ± 0.38 kg (P = 0.0001), 51.7 ± 2.1 cm (P = 0.3), and 39.7 ± 1.1 weeks (P = 0.6). Pregnancy complications in group 1 were detected in 63% (preeclampsia – 34.8%, iron deficiency anaemia (IDA) 4.3%, infections 8.7%, and threatened miscarriage 15.2%) in group 2 – 32.5% (preeclampsia 17.8%; IDA 14.8%) (P = 0.0001); chronic intrauterine fetal hypoxia – 34.8 and 5.9% (P = 0.0001); complications in delivery – 35.6 and 20.7% respectively (P = 0.049). Parent's obesity of study group were noted in 75.9% of cases, control 1.8% (P = 0.0001). There were no significant differences between the groups in the nature of delivery, pregnancy, and delivery account; parental smoking.
Conclusions
Large birth weight, complications of pregnancy (preeclampsia, infections, and threatened miscarriage) and delivery, chronic intrauterine fetal hypoxia; obese parents are related to perinatal risk factors for obesity development in adolescence.

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P805

Morbidity dynamics of diabetes in children living in the West region of Belarus

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Introduction
Diabetes is an urgent medical and social problem. This disease has a prevalence of features of the epidemic, which covers the majority of economically developed countries. Complications of diabetes are the cause of early disability and high mortality of children. Incidence of diabetes among children is significantly different in different countries. The highest incidence rates observed in the Scandinavian countries. Countries with low incidence – Chile, Mexico, and China. Belarus indicated an average incidence of diabetes.
Aim
To evaluate the dynamics of morbidity with diabetes in children living in the western region Belarus, for the period from 2002 to 2012. Identify the influence of various factors on the development of diabetes in children.
Materials and methods
An analysis of 75 outpatient children aged from 1 to 15 years, suffering from diabetes and living in the Western region of Belarus. By according to statistical reports of the dynamics of morbidity in children over the past 10 years.
Results
Over the past 10 years has increased the number of children with diabetes, with 46.3 cases/100 000 children to 70.1 cases/100 000 children. Of these, new cases in 2002 was 7.6/100 000 children, in 2012 – 13.4/100 000 children. With age, number of children with diabetes, increased from 15.5 to 135, 8/100 000 children. Most children (96.0%) suffering from type 1 diabetes. Girls suffer more likely than boys (60 and 40% respectively, P < 0.05). In 85.3% of cases beginning disease have been associated with respiratory infections child, 6.5% of cases the disease was associated with transferred psychological stress. 60% of children fall ill diabetes in the winter and 26.7% of children – in autumn period. Only 8.0% of the cases was a family history of diabetes.
Conclusion
Thus, for the period from 2002 to 2012 incidence of diabetes in children living in western region of Belarus grew by 1.5 times. Girls suffer from diabetes than boys. The main cause of illness onset diabetes is respiratory infection. In this connection, to prevent diabetes should be active prevention of children's respiratory infections in autumn winter period.

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P806

25-Hydroxyvitamin D concentrations before and in the 1st year of GH treatment in relation to height velocity, IGF-1 and bone age

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Introduction
The start of GH (rhGH) treatment in children with GH deficiency (GHD) causes a significant increase in bone turnover and increases height velocity. The increase in IGF1 concentrations during rhGH treatment is a marker of the efficiency of treatment. Bone age delay at baseline is related to GHD and is a good predictor of height velocity during treatment. A significant increase in bone turnover during rhGH treatment results in an increased demand for vitamin D. It is important to determine proper supplementation doses of vitamin D in patients during catch-up growth.
Aim of study
The aim of the study is to evaluate the correlation between IGF1, bone age and 25-hydroxyvitamin D at baseline and in the 1st year of rhGH treatment, and height velocity before and during rhGH treatment.
Material and methods
The study group consisted of 76 children aged 3–16 years with GHD. IGF1 and 25-hydroxyvitamin D concentrations, bone age, and anthropometric parameters were measured at baseline and during 12 months of treatment.
Results
Vitamin D status at baseline correlated with height velocity before rhGH treatment (P < 0.05, r = 0.49). The mean 25-hydroxyvitamin D concentration at baseline was 19.57 ng/ml (±6.19 s.d.) and after 12 months of rhGH treatment

with vitamin D supplementation it increased to 24.1 ng/ml (±6.88 s.d.). A negative correlation between Δ25-hydroxyvitamin D and ΔIGF1 ($P<0.05$, $r=-0.38$) was found.
Conclusions
Vitamin D status is related to height velocity and adequate vitamin D supplementation is important in patients with GHD during catch-up growth, when their bone turnover is increased as a result of rhGH treatment. Determining proper supplementation doses of vitamin D in such cases requires further research.

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P807

Usefulness of ACTH stimulation in the differential diagnosis of precocious pubarche

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Introduction
Nonclassical congenital adrenal hyperplasia (NCCAH) is caused by reduced 21-hydroxylase activity, leading to excessive adrenal androgens and premature pubarche (PP); idiopathic PP (IPP) is its main differential diagnosis. The gold standard for the differential diagnosis is ACTH stimulation test (ST); this test also estimates the adrenal cortisol reserve in NCCAH patients.
Objectives
To compare the clinical characteristics and baseline hormonal profile of patients with PP; to determine the importance of ST in the differential diagnosis between IPP and NCCAH and in the evaluation of the adrenal production of cortisol.
Methods
Retrospective study of patients with PP starting after 2 years of age who underwent ST.
Results
43 patients were included; median age at diagnosis was 7.5 years (range: 3.5–9.4), 37 (86.0%) were females. After ST, 37 (86.0%) were classified as IPP and 6 (14.0%) as NCCAH. No significant differences could be found in the clinical characteristics and baseline determination of ACTH, cortisol, and adrenal androgens between the groups. Both basal and stimulated 17-OHP levels were significantly higher ($P=0.001$ and $P<0.001$ respectively) in NCCAH patients (basal: 4.62±3.70 ng/ml (0.80–10.50); stimulated: 35.41±24.87 ng/ml (12.0–80.2)) than IPP patients (basal: 1.04±0.77 ng/ml (0.22–3.80); stimulated: 4.18±1.71 ng/ml (1.0–8.96)). Nevertheless, the proposed cut-off level (<2.0 ng/ml) for the distinction between the groups, did not allow for this in two NCCAH patients that were only diagnosed after ST. Two NCCAH patients (33.3%) had stimulated cortisol levels <18 μg/dl, showing the need for glucocorticoid stress therapy. NCCAH patients with higher initial 17-OHP value had a lower cortisol after stimulation ($P=0.004$, $r=-0.43$).
Conclusion
The ST was useful to distinguish between patients with NCCAH and IPP, for no basal 17-OHP level could allow for a definitive differential diagnosis in the individual patient. In some NCCAH cases, it also showed inappropriate cortisol secretion under stress, contributing to the therapeutic decision.

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P808

Peculiarities of emotional disorders in children with obesity

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Background
Social adaptation difficulty is one of the serious complications in obese children. It manifests with the complex of emotional and behavioral disorders.
Aim
To estimate the peculiarities of psychological status, frequency, and severity of depressive disorders in obese children.
Methods
We examined 242 children in the in the Endocrinological Department of University Hospital (Minsk); group 1 – 152 obese children (BMI 33.4±4.07 kg/m^2, 14.63±1.7 years), group 2 – 90 normal-weight controls (BMI 20.5±1.47 kg/m^2 ($P=0.0001$), 14.5±1.5 years ($P=0.6$)). All children and their parents underwent psychological testing: (Children Eating Disorder Examination Questionnaire) ChEDE-Q, (Depression Self-Rating Scale) DSRS, and (Child Behavior checklist) CBCL. Results were processed using SPSS.18.
Results
The reliable differences on CBCL testing were in obese children vs controls – anxious and depressive scale ($P=0.002$), impulsiveness scale ($P=0.009$), estrangement scale ($P=0.0001$), and attention deficiency scale ($P=0.001$). The frequency of depressive disorders (DSRS) were in 18.1% obese children. The severity of depressive symptoms didn't correlate with BMI. Clinical depression correlated with compulsive symptoms severity (CBCL) ($P=0.02$). Binge eating (BE) disorders were diagnosed in 20% obese children ($P=0.016$). The reliable difference between BE and age, gender, BMI didn't noted ($P=0.3$–0.06). We can say with the probability of 99% ($P=0.002$ and 0.004) that compulsive mechanisms of BE in obese children are determined with the presence of emotional disorders (anxious and depressive symptoms and estrangement).
Conclusions
The reliable increase in the frequency of psychological and behavioral disorders were noted in obese children in comparison with normal-weight control.

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P809

Emotional and binge eating disorders in children with severe obesity

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Background
Binge eating (BE) is a common cause of severe paediatric obesity, which develops after the uncontrolled wish of changing the present emotional condition.
Aim
To study the phenomenon of BE in the context of emotional disorders in severe obese children.
Methods
We examined 88 children with severe obesity (mean±s.d. 11.5±3.4 years; BMI 29.7±5.7 kg/m^2) in the Endocrinological Department of University Clinic (Minsk) and 50 healthy controls (10.6±2.3 years ($P=0.4$), BMI 17.3±2.3 kg/m^2 ($P=0.01$)). Eidemiller test (ET) underwent 88 obese and 17 controls; (Children Eating Disorder Examination Questionnaire) ChEDE-Q, (Depression Self-Rating Scale) DSRS, and (Child Behavior checklist) CBCL – 70 obese and 50 controls.
Results
ET showed the reliable excessive demands ($P=0.004$), educational uncertainty ($P=0.001$), imposition the conflicts on child ($P=0.049$) parents of obese patients. DSRS showed the presence of clinical depression in 8.3% obese and 5.3% healthy children. There were the reliable differences between depression and BE symptoms by CBCL ($P=0.002$). BE were noticed in all examined children with obesity by ChEDE-Q test ($r=0.57$, $P<0.01$) and had a strong relation with the clinical symptoms of attention deficiency ($r=0.57$, $P<0.01$) and hyperactivity/impulsiveness ($r=0.56$, $P<0.01$).
Conclusions
We found the presence of BE disorders with attention deficiency and hyperactivity/impulsiveness in obese children. Parent's excessive demands, educational uncertainty and imposition the conflicts on the child might be one of the cause of obesity development in children. Improving these psychological problems is the effective treatment of obese children

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P810

Effect of microelement imbalance on the thyroid function in children

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Biological significance of microelements depends on concentration and interaction between them. Children are more sensitive to micronutrients imbalance. The aim was to estimate the microelement imbalance influence on the thyroid gland function and physical, mental and intellectual development of the children.

Growth and weight were estimated by CDC 2000, psychological status from birth by the skills and speech development, from 8 years by Luscher, Kos, Schulte, verbal, drawing, and correction tests, IQ Raven's test; thyroid gland ultrasound; TSH, fT_4, fT_3, and TPO-Ab by IEA; urinary iodine by kinetic cerium-arsenical method; hair analysis for metals by ICP-mass spectrometry; methods of descriptive and nonparametric statistics.

Were examined 74 children aged 9 years living in environmentally disadvantaged region of the Tatarstan Republic (Nizhnekamsk). They were divided according to the cut-off point of lead concentration 5 mg/kg into two groups: main group, $n=18$ (≥ 5 mg/kg) and the comparison group, $n=56$, (<5 mg/kg). Control group consisted of apparently healthy children from Kazan ($n=30$).

Elevated lead correlated with a cadmium valid increasing ($P<0.003$). Elevated concentrations of lead and cadmium reliably correlated with urinary iodine decreasing ($P<0.0001$) and TSH increasing ($P<0.02$). Medians of thyroid hormones were: TSH, 3.82 and 2.05 mU/l ($P<0.001$), fT_4-16.2 and 14.8 pmol/ml, fT_3, 12.1 and 8.41 pg/ml ($P<0.01$) in the main and control groups respectively. 75% of the main group had a height below the 25th percentile, 73.3% of the control group had a height between 50 and 75th percentiles. The average IQ was 101.2 and 112.6 ($P<0.02$) in the main and control groups respectively. The main group has a significantly decreased logical, visual memory, attention and increased emotional lability, anxiety, and alexithymia.

The possible mechanisms of iodine and lead, cadmium, cobalt, nickel, copper, and zinc interactions may cause the thyroid gland dysfunction, and as a result, the delay of physical, mental and intellectual development of the children.

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P811

Further molecular characterization of a novel neurodegenerative syndrome associated to a mutation in the Seipin/*BSCL2* gene

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Mutations in the Seipin/*BSCL2* gene cause either type 2 congenital generalized lipodystrophy (BSCL) or dominant motor neuron diseases. However, we recently discovered a c.985C>T mutation in the *BSCL2* gene that results in a novel fatal neurodegenerative syndrome (celia encephalopathy). This mutation induces an alternative splicing which results in skipping of exon 7 and a reading frame shift (Guillen-Navarro *et al*. 2013 *J Med Genet* **50** 401–409).

Homozygous patients suffer from progressive encephalopathy since ages 2–3 years, with fatal outcome at ages 6–8 years; however, carriers for the c.985C>T mutation are asymptomatic, conflicting with the gain of toxic function attributed to the mutation. Our previous studies showed a partial nuclear localization of wt and exon 7 skipped seipin. This location might be related to the presence of intranuclear ubiquitin-positive inclusions in brain tissue from a homozygous patient (index case), which are likely to consist of misfolded, aggregated mutant seipin. Besides, ER stress in cells expressing exon 7 skipped seipin was also found. Here we report further molecular characterization of exon 7 skipped seipin. Using density gradient ultracentrifugation, we found that wt seipin oligomerizes forming tetramers according to calibration with a set of proteins of known MW. We also found that exon 7 skipped seipin forms much larger aggregates under similar conditions, corresponding to dodecamers. We hypothesized that wt and exon 7 skipped seipin might interact and form mixedoligomers. Given that levels of wt seipin expressed by heterozigous individuals are substantially higher than those of exon 7 skipped seipin, we reasoned that wt seipin might rescue the phenotype by recruiting exon 7 skipped seipin into mixed normal size oligomers, thus impeding their aggregation into larger, presumably toxic, and oligomers. We therefore expressed wt and exon 7 skipped seipin at a 3:1 ratio in HeLa cells and performed density gradient ultracentrifugation of cell extracts. We found a change in the pattern of distribution of each of the seipin isoforms, with exon 7 skipped seipin emerging at earlier fractions. This result clearly indicates the interaction between both seipin isoforms through the formation of mixed oligomers.

Together, our findings provide a clue about the origin of the intranuclear aggregates observed in neurons from the index case, and offer a possible explanation of the absence of phenotype in heterozygous mutation carriers (funded by Consellería de Industria (Xunta de Galicia), 10PXIB208013PR and ISCIII-FEDER PI10/02873).

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P812

Pediatric Graves disease: treatment options and prognosis factors

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Introduction

Graves' disease (GD) is the most common cause of hyperthyroidism in children. Therapeutic options available (anti-thyroid drugs, radioactive iodide, and thyroidectomy) are associated with complications and treatment of this age group remains controversial.

Objective

To review our experience in the management of pediatric patients with GD.

Materials and methods

Retrospective review of 35 children, diagnosed between 1984 and 2010, at Pediatric Endocrinology Unity of CHUC.

Results

35 children followed, 85.7% females, 11.3 ± 2.5-year-old (7–18), 53.3% prepubertal. Anxiety (60%), goiter (60%), weight loss (45.7%), tremor (42.9%), palpitations (34.3%), and exophthalmos (37.1%) were the most frequent initial manifestations. Mean duration of symptoms of 11.3 ± 2.5 months. Analytically, increased FT_4 in 88.9% (mean 4.1 ± 1.4 ng/dl; normal: 0.8–1.9), FT_3 in 94.4% (mean 12.9 ± 5.8 pg/ml; normal: 1.4–4.4), supressed TSH in 96.9%. TRAbs were positive in 91.1% (P50 13.3 IU/l, normal: <1). All children started anti-thyroid drugs, 68.9% methimazole (mean 0.4 mg/kg/weight/day), and 31.4% propylthiouracil (mean 5.4 mg/kg/weight/day). No severe side effects recorded. After normalization of thyroid hormones levothyroxine was started in 85.7%, on average 3.8 ± 2.9 months after initiation of medical treatment. During follow-up: 10 (28.6%) children were in remission after 29 ± 11.4 months of medical treatment, 6 (17.6%) underwent thyroidectomy and 4 (11.8%) to radioactive iodide after 25. 7 ± 15.9 months of treatment. 14 children still maintain medical therapy for 22.3 ± 11.4 months. In children who underwent definitive therapy (surgery or radioactive iodide) there was a significant difference in duration of symptoms (9.3 ± 7.1 vs 3.8 ± 2.0 months, $P=0.035$), FT_4 levels (4.7 ± 1.2 vs 3.1 ± 1.2 ng/ml, $P=0.041$), and FT_3 (15.4 ± 3.1 vs 8.8 ± 4.9 pg/ml, $P=0.056$).

Conclusion

In this series, medical treatment remained the initial option for all patients. Remission rate was 28.6% after an average of 2.5 years of treatment with anti-thyroid drugs. Diagnostic delay as well as higher levels of FT_4 and FT_3 at presentation were associated with unlikelihood of remission and the need for a definitive treatment.

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Polycystic ovary syndrome in overweight and obese adolescent girls and its association with insulin resistance and metabolic syndrome

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Background

The prevalence of polycystic ovary syndrome (PCOS) in adolescents is reported up to 38.9%. Obesity is a known risk factor associated with PCOS increasing the risk of metabolic syndrome (MS). Up to 25% of adolescents with PCOS may have derangements in glucose metabolism and insulin resistance (IR).

Aim

To evaluate PCOS prevalence in overweight/obese adolescent girls and to assess the association with BMI, MS and IR.

Methods
49 overweight and obese adolescent girls at least 2 years post menarche were included in the study (mean age 15.75±1.3 years). Mean BMI–SDS was 2.36±0.9.
PCOS was diagnosed according to Rotterdam criteria.
MS was diagnosed according to IDF consensus for MS in children.
Results
PCOS was identified in 36.7% of overweight/obese adolescent girls.
Girls with PCOS had lower BMI–SDS (1.9±0.7 vs 2.62±0.9, $P=0.004$), waist circumference SDS (0.9±0.6 vs 1.5±0.7, $P=0.009$) and sum of skinfold thickness (93.4±27 vs 111.9±25 mm, $P=0.02$) comparing to girls without PCOS.
24.0% of girls without PCOS had polycystic ovary morphology on ultrasound, normal menstrual cycle and normal androgen levels. Polycystic ovaries by ultrasound were found in 83.3% of girls with PCOS.
MS was found in 17.6% of girls with PCOS compared to 30.0% in girls without PCOS ($P>0.05$).
Insulin resistance HOMA–IR index and fasting glycaemia did not differ in girls with and without PCOS ($P=0.08$). High density lipoproteins were significantly higher in girls with PCOS ($P=0.04$).
Conclusions
Every third overweight/obese adolescent girl has PCOS. The prevalence of MS in overweight/obese girls is not increased in the presence of PCOS or polycystic ovary morphology. The degree of IR is similar in overweight/obese adolescent girls with and without PCOS.
PCOS or polycystic ovaries by ultrasound do not increase the MS rate.

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P814

Differences in skeletal development and growth in children with Noonan syndrome

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Background
Noonan syndrome (NS) is a genetic multisystemic disorder secondary to mutations in Ras/MAPK pathway, essential for cell's differentiation and growth, patients associating short stature and skeletal anomalies. We describe the alterations in bone development and growth in five children with NS, four of which received treatment with recombinant human GH (rhGH).
Methods
We reviewed the cases of five children with NS (three boys, two girls, aged between 5 and 13 years), evaluated at the endocrinology department between January 2010 and January 2014. Clinical and hormonal data, calcium metabolism, as well as osteodensitometric and radiographic bone assessment were documented.
Results
All children had specific phenotype for NS, three of them having molecular confirmation (*KRAS*, *PTPN11*, and *SOS1* mutation). All had short stature, with a mean height of −3.27 s.d.. Hand–wrist radiography showed moderately delayed bone age. BMD/DXA was performed in four children and revealed osteopenic *Z*-score in all cases. None of the patients had congenital bone deformities described at birth, but one with *SOS1* mutation had a major scoliosis with a double curve diagnosed at age 2 and did not received treatment with rhGH. All patients treated with rhGH had a good growth respose with mean height velocity between 0.55 and 0.70 cm/month in 24 months interval. The most frequent skeletal anomaly was chest deformity: inferior pectus excavatum and/or superior pectus carinatum, present in all patients. Other bone anomalies included: cubitus valgus, varus equin foot, and slightly shortness of fingers and toes and these features do not contraindicate the treatment with hGH.
Discussions
Disorders of RAS/MAPK pathway have an overlapping skeletal phenotype suggesting its importance in bone homeostasis. All patients with NS had short stature with late bone development and different skeletal deformities. rhgh treatment is very important in these children and the earlier initiation of therapy, the greater growth optimization is possible.

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P815

Short stature and carnitine deficiency: the hidden connection

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Introduction
Lipid storage myopathy (LSM) is characterized by increased lipid droplets in muscle fibers. Primary carnitine deficiency is the most frequent cause of LSM, clinical presentation ranging from asymptomatic to progressive muscle weakness or cardiomyopathy, carnitine supplementation being effective with remission of symptoms.
Case report
In February 2007 R.A. born in 1996 presented progressive muscle weakness with elevated muscular enzymes (LDH=1155 UI/ml, $n=125–234$, and CPK=1082 UI/ml, $n=25–195$). Starting from a muscular biopsy, which suggested polymyositis, a glucocorticoid trial was initiated with partial amelioration followed by clinical relapse. Development of Cushingoid syndrome and growth retardation (height 123 cm, −3 s.d.; weight 22 kg, −2.5 s.d.; normal parental heights) determined endocrinological evaluation which revealed normal IGF1 (172 ng/ml, $n=111–551$), and basal GH (3.3 μUI/ml) with response at stimulation (stimulated GH 125 μUI/ml) and delayed bone age of 8.5 years. Functional pituitary evaluation was normal. Reevaluation by muscular biopsy revealed presence of increased lipid droplets in type 1 muscle fibers suggesting LSM. Carnitine supplementation was started in December 2008 and continued without pause (1 g/day) with progressive clinical improvement and normalization of muscular enzymes.
Absence of GH deficiency justified expectative but the stagnant height after 6 months was an argument for hGH therapy, which was started in October 2008 followed by a satisfactory growth rate (∼0.5 cm/month). Reevaluation in July 2013 revealed Tanner pubertal stage IV, height of 153 cm (−1.95 s.d.) and delayed bone age of 14 years.
Conclusion
We report a patient with short stature and LSM who responded well to hGH therapy and carnitine supplementation. To our knowledge, children with LSM do not usually associate short stature or GH deficiency. Impact of hGH therapy on body composition and muscle structure in LSM cases needs to be further evaluated.

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P816

Nonalcoholic fatty liver disease in obese children

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With the increasing prevalence of obesity in children, there is a growing number of its comorbidities as nonalcoholic fatty liver disease (NAFLD).
The aim of this study was to evaluate the prevalence of NAFLD in a group of obese patients and to identify additional risk factors for NAFLD development in the examined population.
Materials and methods
We examined 88 obese children (41 boys) mean age 14.4 (±2.6) hospitalized in our department in 2013. The analysis evaluated anthropometric parameters, body composition, calculated indicators: BMI, waist:hip ratio (WHR), waist:height ratio (W/HtR), and the components of the metabolic syndrome (MS). The assessment of liver function and steatosis was assessed by ALT and ultrasound respectively.
Results
MS was diagnosed in the 26 (29.54%) of children. 24 (27.27%) of patients had fatty liver on ultrasound. MS was more often diagnosed among children with hepatic steatosis compared to a normal liver group (50 vs 27.2%). Among the anthropometric parameters only WHR significantly correlated with the occurrence of fatty liver in the ultrasound image. Liver hyperechogenicity level correlated significantly with fasting insulin level, insulin and glucose in 120 min of OGTT and HOMA–IR index. There was the significant correlation between concentration of ALT and the sum of the MS components.
Conclusions
Obese children who met MS criteria have to be screened for the NAFLD. Hyperinsulinemia and insulin resistance seem to be the prognostic factors indicating rigorous liver function assessment in obese children.

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P817

Hormone and metabolic profile of diabetic adolescent girls with menstrual disorders

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The aim of the study was to evaluate hormonal profile in diabetic adolescent girls with menstrual disorders and compare them to regularly menstruating diabetic and healthy girls.
We studied 54 adolescent girls with T1DM treated with intensive and continuous insulin therapy in the chronological age of 15.9±1.3 years and gynecological age of 33.7±16.7 months with the mean HbA1c for the last year 7.4±1.5%. In 18 (33%) girls menstrual disturbances (MD) were present (amenorrhea in three, oligomenorrhea in seven, and irregular menses in eight), while 36 (67%) of girls experienced regular menses (RM). 24 healthy girls with regular menses served as a control group (CG). In each subject hirsutism was evaluated, transabdominal ultrasound of the ovaries was performed and concentrations of gonadotropins and androgens were measured.
Difference between mean HbA1c from the beginning of T1DM and for the last year as well as daily insulin requirement in both diabetic groups were statistically insignificant ($P>0.05$). The occurrence of hirsutism (1 (6%) MD vs 2 (6%) RM vs 2 (8%) CG, $P>0.05$), polycystic ovary morphology (9 (50%) MD vs 12 (33%) RM vs 11 (42%) CG, $P>0.05$) and hyperandrogenaemia (4 (22%) MD vs 12 (33%) RM vs 11 (42%) CG, $P>0.05$) were similar in all three groups studied. Only 3 (17%) girls from MD group fulfilled the criteria of PCOS by Androgen Excess Society for adolescents. There were no significant differences between the two diabetic groups with respect to the concentration of gonadotropins, estradiol, and androgens except for higher androstenedion in RM vs. MD (2.2±1.0 vs 2.5±1.4 ng/ml respectively, $P=0.03$). The occurrence of the menstrual disorders correlated only with the age of the first menarche ($r=0.3$, $P=0.02$).
It is concluded that in diabetic girls menstrual disturbances do not seem to be associated with increased hyperandrogenemia and PCOS incidence is similar to that in general population (6%).

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Analysis of Th17 cells and IL17, IL23 cytokines in peripheral blood from children with autoimmune thyroid disease

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Up till now, altered balance of T helper 1 (Th1) and Th2 immune cells has been postulated to play an important role in the pathogenesis of autoimmune thyroid diseases (AITD). However, recent studies on thyroid diseases suggest a new role for Th17 (T helper 17) cells which have the ability to secrete cytokines: IL17, IL17F, IL21, and IL23. The aim of the study was to estimate the proporcions of circulating CD4+CD161+CD196+ and CD4+IL17+ Th17 cells and serum concentrations of IL17 and IL23 in patients with Graves' disease (GD, $n=42$, mean age±S.E.M. 14.3±4 years), Hashimoto's thyroiditis (HT, $n=37$, mean age±S.E.M. 15±2 years) and in healthy controls (C, $n=25$, mean age±S.E.M. 15.2±2 years).
Polychromatic flow cytometry and several fluorochrome-conjugated MAbs were applied to delineate Th17 cells using apparatus FACSCalibur (BD Biosciences). In untreated HT children we observed an increased percentage of CD4+CD161+CD196+ (7.1±3.5 vs 3.7±1.8; $P<0.04$) and CD4+IL17+ (3.7±2.7 vs 1.4±0.4; $P<0.01$) Th17 lymphocytes in comparison to the healthy controls. In GD children we did not reveal such abnormalities in the population of these cells. In untreated patients with AITD we observed an increased levels of IL23 in comparison to control group (GD: $P=0.004$ and HT: $P=0.046$). Methimazole treatment in GD led to decrease these cytokine levels in a period of 6–12 months. However, during 6–24 months of l-thyroxine therapy in HT there wasn't any reduction of IL23 concentration compared with HC. IL17 was elevated only in HTpatients in comparison to the controls (17.17±10.49 vs 11.38±2.99, $P=0.021$), which normalized during therapy. We conclude that the increased percentage of Th17 cells and elevated level of IL17 and IL23 cytokines in children with HT can suggest their role in initiation and development of immune and inflammatory processes in this endocrinopathy.

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P819

Pseudohypoparathyroidism: challenging diagnosis due to autism and epileptic seizures

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Pseudohypoparathyroidism (PHP) is an uncommon sporadic or inherited genetic disorder subdivided into several distinct entities characterized by parathyroid hormone (PTH) resistance in association with distinctive skeletal and developmental defects.
We report a case of a 7 years and 8 months old boy, evaluated at the Endocrinology Department of 'St Spiridon' Hospital Iasi in January 2013, who had a history of hypothyroidism diagnosed at the age of 4 years 6 months (for which he received Euthyrox 50 μg/day) in association with generalized seizures considered to be epileptic (treated with Phenobarbital, brain CT scan performed in 2010 showed calcifications in lenticular nucleus), a delay in language development which lead to a diagnoses of autism, left congenital undescended testis, and hypospadias.
Clinical examination revealed a rounded facies, short neck, flattened nasal pyramid, delayed teeth development with bad implantation, a brachymetacarpia of the fifth finger in both hands, and elements that can be included in Albright's hereditary osteodystrophy (AHO). The boy had short stature (−1.7 S.D.), obesity (+4.4 S.D.), and PI GI pubertal stage.
Biological tests showed hypocalcemia, together with hyperphosphataemia and hypocalciuria but with an elevated PTH level which are arguments that beside clinical findings of AHO strongly advocate for PHP type 1a.
During the following months several therapeutic adjustments (calcium and vitamin D supplementation) were needed to maintain an adequate calcium–phosphate balance and currently the patient has achieved a satisfactory calcium–phosphate homeostasis.
Conclusions
The present case highlights the difficulty of an early correct diagnosis of PHP. In this context it is possible that mental retardation and delayed language development may have been due to PHP and seizures could have been the first manifestation of hypocalcaemia. We underline the importance of a complete biochemical investigation of the calcium–phosphate metabolism to recognize typical biochemical alterations associated with this condition together with the phenotypic aspect that often escapes to be noticed.

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P820

Anti-oxidation improves in early puberty in normal weight and obese boys, in positive association with exercise stimulated GH secretion

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Oxidative stress in humans has been associated with obesity. Puberty is a maturation period characterized mainly by changes of the GH and the gonadotrophin hormones secretion. To investigate the possible association of

the GH and the hypothalamic–pituitary–gonadal (HPG) axes before and during early puberty, with the pro- and anti-oxidation mechanisms 76 healthy, pre-pubertal normal weight ($n=28$), pre-pubertal obese ($n=11$), early pubertal normal weight ($n=25$) and early pubertal obese ($n=12$) male pupils of the 5th and 6th grades of an elementary school were studied at baseline and after a sub-maximal exercise protocol (on a stationary cycle ergometer) at 70% VO_2max. All subjects underwent blood sampling before and after this exercise bout for measurement of pro- (thiobarbituric acid reactive substances (TBARS) and protein carbonyls (PCs) and anti- (glutathione (GSH) and the oxidized glutathione disulfide (GSSG), the GSH:GSSG ratio, the enzymes glutathione peroxidase (GPX) and catalase and total antioxidant capacity (TAC)) oxidation markers and hormones (GH, IGF1, IGFBP3, FSH, LH, and testosterone).
Baseline and post-exercise TBARS and PCs were significantly greater while baseline GSH, GSH:GSSG, and TAC were significantly lower in obese than in normal weight subjects. Baseline and post-exercise GPX was significantly lower in obese than normal weight pre-pubertal subjects. GH and testosterone concentrations were lower in early pubertal obese compared to normal weight subjects. Early pubertal subjects demonstrated greater amounts of TAC than pre-pubertal ones at baseline. Following the exercise bout, TBARS, PCs, GSSG, TAC, catalase, and GPX increased while GSH and the ratio GSH:GSSG decreased in all studied groups. GH concentrations increased following exercise in early pubertal subjects. Multiple regression analysis of all subjects, revealed statistically significant positive linear regression between the exercise-associated GH increase and that of GSSG. In all studied subjects baseline GH was the best negative predictor for post-exercise PCs. Baseline waist circumference was the best negative and positive predictor for post-exercise concentrations of GPX and for TBARS respectively.
In conclusion, moderate acute aerobic exercise is a good model for the study of the pro- and anti-oxidation mechanisms. Obese subjects demonstrate greater pro- and lower anti-oxidation mechanisms than normal-weight subjects while also demonstrating lower GH concentrations in early puberty. These observations highlight the deleterious potential of obesity. The anti-oxidant capacity of the organism seems to improve with puberty along with the potentiation of the exercise-associated GH increase.

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P821

Molecular findings of three different male under virilization cases with 47,XXY karyotype

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Introduction
Male under virilization is a rare condition mostly due to the mutations of hormones that effect male reproductive tract. One of the most important gene mutations that effect that pathway is the androgen receptor gene (AR) mutations which is located at Xq12 in individuals with 46, XX. In this report, we present the *AR* and *SRD5A2* gene analysis of three different under-virilized patients with 47, XXY karyotype.
Methods
Chromosome analysis of the patients were assessed by standart lymphocyte karyotype, with Giemsa staining. PCRs were carried out by amplifying all the exons of related genes, and direct sequencing protocol was applied for mutation detection.
Results
One of the patients had no mutation in *AR* and *SRD5A2* genes, but had a 23 repeat polymorphism on exon 1 of *AR* gene. The second had no mutation in *AR* gene, had a 22 and 23 repeats polymorphism, but had a homozygous p.G196S mutation in *SRD5A2* gene. The third had a heterozygous mutatin in p.F891L in *AR* gene, with a 16 and 21 repeat polymorphism, and had no mutation in *SRD5A2* gene.
Discussion
47, XXY karyotype is a very rare condition in male virilization cases. Mutations in *AR* gene, in addition with *SRD5A2* gene, are thought to be the common reasons of this condition. According to our results, we suggest that not only the *AR* gene analysis, but also *SRD5A2* gene analysis and polyGLN polymorphism of the exon 1 of *AR* gene have important impacts for the diagnosis of male under virilization.

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P822

Achondroplasia and neurological complications

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Achondroplasia is the most common genetic causes dwarfism. Its prevalence is 1/10 000 à 30 000 birth. it is an autosomal dominant disease associated with the mutation of the receptor gene growth factor on chromosome 4p16 fibroblastes FGFR3 responsable rhizomelic dwarfism and multiple complications likely to compromise the functional and vital prognosis of patients.
Aim
Find the frequency of neurological complications and identify scalability.
Patients and methods
Twenty patients with achondroplasia were hospitalized in our departments between 2000 and 2013. In addition to clinical examination, paraclinical was performed with X-rays of the skeleton, brain and spinal MRI.
Results
The mean age of patients was 7 ± 1.4 years. Six patients had an age ≥ 15 years. The neurological examination were normal in all cases. 33% had a non-active hydrocephalus and without repercussion. One patient had a narrowing of the foramen magnum by atlondo – odantoidienne hypertrophy and narrowing of the foramen magnum requiring only supervision. A narrowing of the spinal canal observed in a patient aged 16 years old.
Discussion and conclusion
Achondroplasia is a disease of the constitution of the bone that reduces the number of functional fibroblast. Bone growth is done in the width direction and at the spine, the vertebrae may cause growth of a narrowing of the spinal canal with risk of compression and hydrocephalus. There are possibilities of brain and spinal neurological complications which must be systematically sought particularly in adulthood.

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P823

Pediatrics cushing disease: a diagnostic challenge

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Introduction
Cushing's disease (CD) is rare in children. It's most common clinical manifestations are growth retardation, changes in pubertal development and weight gain. The diagnosis, based on clinical suspicion, is often hampered by the non identification of the microadenoma in MRI.
Clinical history
A 14-year-old male patient, with short stature, growth arrest after 12 years and weight gain since age of 9. At physical examination, he had moon face, facial flushing, acne, abdominal obesity. BP 131/75 mmHg (P95), weight 54.5 kg (P75), height 135 cm ($\ll$P3), BMI 29.9 kg/m^2 ($>$P95), Tanner: P2, A1, G1. Bone and chronological age were similar.
Etiologic study and evolution
Thyroid function, IGF1 and prolactin were normal, FSH 0.33 mIU/ml and LH <0.1 mIU/ml. Androgens were compatible with Tanner stage 2. Urinary 24 h cortisol was increased (1.9–8 times normal) and had absent cortisol circadian rhythm (serum cortisol at 23 h: 9.74 µg/dl). High-dose dexamethasone suppression test detected 52.2% reduction in serum cortisol, suggestive of ACTH dependent Cushing's syndrome. Pituitary MRI and adrenal CT were normal. Hypercortisolism persisted and after 16 months pituitary MRI was still normal. Inferior petrosal sinuses catheterization was suggestive of CD and the pituitary MRI, 8 months later, revealed a slight pituitary asymmetry, with a 2.5 mm hyperintense area on T2. He was submitted to transphenoidal surgery with apparent removal of the tumor. Histological result was normal pituitary tissue. In spite of that, the patient had decreased weight, resumption of growth and adequate pubertal development. His final/targeted height was 151/164 cm ($P \ll 3$/P10). Three years after surgery, he remains in clinical and analytical remission.
Discussion
This case had a successful evolution, but highlights the difficulties of CD diagnosis in children. Time between clinical suspicion and definitive treatment

can be long, and the therapeutic decision must take into account all the risks and benefits involved.

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P824

Metabolic repercussion of growth hormone deficiency in the child and adolescent

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Introduction
GH deficiency cause a short stature in the child. In the adult hood, other complications appear: An increase of cardiovascular mortality due to an atherogenic profil of lipids and glycaemia abnormalies is reported
Aim
Search metabolic disorders in children and adolescents presenting GH deficiency
Materials and Methods
Patients (56 boys, 36 girls) follow up in our consultation for deficit in GH (Diagnosed on clinical and biological elements: absence of response of the GH to test of stimulation: glucagon-propanolol and insulinic hypoglycaemia. We treated in an irregular way by the recombining GH (cost, availability).
The average age at the diagnosis is 10,8 years in the boys (1-19) 6.5 years in the girls (1-17,5). Mean duration of treatment 4,8 years.
The GH deficiency is isolated in 63 patients; associated to thyreotrop deficiency in 16 cases and corticotrop deficiency in 13 cases.
All the patients are a metabolic assessment: Fasting glycaemia and postprandial at the teenagers (superior at 15 years: n = 10). A lipid assessment: total cholesterol and triglycerides.
Results
An asymptomatic fasting hypoglycaemia: 10/92 (10,86%).
A moderate fasting hyperglycaemia: 5/92 (5,5%).
A diabetes mellitus: 1/92 (1,2%).
A mixed hyperlipidemia: 3/92 (3,2%).
A hypercholesterolemia: 1/92.
A hypertriglyceridemia: 1/92.
Conclusion
Our results confirm those of the literature. The metabolic disorders in the GH deficiency in children is generally appeared 10 years after the installation of the affection among patients badly substituted. They can be worsened by other pituitary deficits. A retreat and a more important recruitment are necessary to consoled our results.
A regular treatment by the growth hormone and a rigorous follow up are necessary for improved the vital fore cast.

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P825

Medication safety study investigating hydrocortisone individually and extemporaneously compounded capsules for paediatric use in congenital adrenal hyperplasia

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Background
Treatment outcome with hydrocortisone for congenital adrenal hyperplasia (CAH) in neonates and children is highly variable. As there is no licensed formulation for children <6 years hydrocortisone capsules individually have to be compounded by local pharmacies (dose strength: 0.5–9.5 mg). The aim of this study was to characterise mass and content of these capsules in order to assess medication safety for effective and nontoxic dosing in terms of precision of mass and drug concentration as well as accuracy of drug content in the compounded capsules.
Methods
20 batches of 20 capsules each were analysed so far according to European Pharma-copoeia[1]. Precision of net capsule mass filling was investigated gravimetrically by substracting the chasing from the total capsule mass. Next, the mean mass per batch and % deviations from mean mass for each capsule were calculated ('mass precision'). For precision of drug content, an HPLC-UV method (Agilent Eclipse XDB C18 column; H_2O: ACN 70:30, v/v) for hydrocortisone concentration was developed and validated[2] also separating fludrocortisone potentially co-com-pounded. Mean concentration per batch was determined; for each capsule % deviation from mean concentration ('content precision') as well as from nominal concentration were calculated ('content accuracy').
Results
Mean concentration of hydrocortisone was 11.7% lower than the nominal one.
Conclusions
Up to 20% of the batches did not meet the accuracy or precision criteria. Hence, therapy might be inadequate in up to every 5th child. The study demonstrates the need for improved medication safety in neonates and infants suffering from CAH.
Acknowledgements
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1. European Pharmacopoeia, 8th ed. (2013),
2. EMA, Guideline on bioanalytical method validation (2012).

	Mass precision (%)		Content precision (%)	Content accuracy (%)
Single deviation ±7.5%/10%[1]	>7.5	Single deviation ±15%[1]	>7.3	38
Single deviation ±15%/20%[1]	>0	Single deviation ±25%[1]	>4.5	8.8
Batches that failed test[1]	20	Batches that failed test[1]	15	20

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Pituitary – Basic (*Generously supported by IPSEN*)

P826

Copeptin concentrations increase during glucagon stimulation test: possible role of copeptin in assessment of anterior pituitary function

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Background
Copeptin, the C-terminal part of the arginine vasopressin (AVP) precursor, is a 39-amino acid peptide stoichiometrically secreted with AVP in 1:1 ratio from the posterior pituitary. In contrast to AVP, copeptin remains stable *ex vivo* for several days in serum or plasma. Here, we investigated the use of the copeptin assay in the diagnostic workup of patients with suspected anterior pituitary dysfunction.
Patients and methods
We measured cortisol, GH, ACTH and copeptin during glucagon stimulation test (GST) in 56 subjects divided into healthy controls (Group 1, $n = 21$), subjects with history of pituitary disease (usually pituitary adenomas), but without evidence of pituitary dysfunction (Group 2, $n = 22$), and those with overt hypopituitarism (Group 3, $n = 13$). Blood samples were taken at 0, 60, 90, 120, 150 and 180 min after i.m. injection of 1–1.5 mg of glucagon.
Results
There were no significant age or BMI differences between groups 1, 2 and 3. Copeptin concentrations at 150 and 180 minutes of GST (in comparison to initial values) were significantly higher in both Group 1 and Group 2 ($P < 0.01$), but remained unchanged in Group 3 (P = NS). In contrast to cortisol, there was a trend towards higher copeptin concentrations in Group 1 *vs* Group 2 (31.25 ± 12.01 *vs* 12.59 ± 3.94 pmol/l (mean ± S.E.M.), $P = 0.06$ and 21.08 ± 6.65 *vs* 12.59 ± 3.94 pmol/l, $P < 0.05$, $P = 0.055$, at 150′ and 180′ of GST respectively). Differences between all subgroups became significant when comparisons were made for area under the curve for copeptin concentrations during multiple measurements. In Group 1 there was a correlation between serum copeptin concentrations and ACTH and cortisol (but not GH) at 150′ and 180′ of GST.

Conclusions
Our data demonstrate that copeptin is released following glucagon stimulation. This raises a possibility that measurements of serum copeptin concentrations might be potentially useful in assessment of anterior pituitary function.

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P827

Effect of ubiquitin/proteosome inhibition on acth secretion by rat corticotropes

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ACTH is the product of proteolytic processing of its precursor, proopiomelanocortin (POMC) and, in turn, is subject to proteolytic degradation. Regulation of proteolysis is crucial to several intracellular processes, including protein activation and inactivation, and thus contributes to active peptide concentrations. The proteosome 26S/ubiquitin system (UPS) is the main, non-lisosomial intracellular proteolytic pathway and alterations to this system have been observed in both neoplastic and degenerative disorders.
Aim of the present study was to evaluate the role of UPS in ACTH turnover regulation within pituitary corticotropes.
Methods
Rat anterior pituitary primary cell cultures were incubated with MG132, an UPS inhibitor, at increasing concentrations (0.001–100 nM) for up to 48 h. Control incubations were performed with plain medium only. Medium and cell content was collected after 4, 24 and 48 h and ACTH quantified by IRMA and western blotting.
Results
Incubation with MG132 was associated with an increase in ACTH secretion at 4 h (0.01 nM: $177 \pm 27.5\%$ control and 1 nM: $129.8 \pm 18.9\%$ control, both $P < 0.05$ vs control wells) and 24 h (0.01 nM: $131.6 \pm 8.1\%$ control, $P < 0.05$ vs control wells). Likewise, an increase in ACTH content was observed after 24 h incubation with MG132 (0.01 nM: $148 \pm 33\%$ control, 1 nM: $187 \pm 33\%$ control, 100 nM: $137.1 \pm 11.3\%$ control, all $P < 0.05$ vs control wells). Western blotting confirmed quantitative data. No significant changes in either ACTH secretion or cell content were observed after 48 h incubation with MG132.
Conclusions
This study demonstrates that the proteosome/ubiquitin system modulates ACTH concentrations within anterior pituitary cells. Further, these results indicate that regulation of ACTH proteolytic degradation contributes to corticotrope secretory activity.

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P828

Different expression of prolactin receptor gene in rat duodenum during physiological and medicamentous hyperprolactinemia

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Introduction
During pregnancy (state with physiological hyperprolactinemia-HP) mothers require larger calcium amount for fetal growth. It has been shown that PRL stimulate intestinal calcium absorption in physiological HP, which can protect mother's skeletal system from further mineral density loss. On the other hand, medicamentous-related hyperprolactinemia is more frequently associated with reduced BMD and increased fracture risk. We conducted the experimental study to evaluate if prolactin receptor (PRLR) gene expression in duodenum differs during physiological and medicamentous hyperprolactinemia.
Methods
Wistar female rats 18 weeks old were divided into: Group P: nine rats, 3 week pregnant; Group M3: ten rats that were i.m. administrated Sulpirid (10 mg/kg) twice daily for 3 weeks; and age matched nulliparous rats as a control group: ten rats, 18 weeks old (C1). Serum PRL concentration was measured using ELISA kit for PRL. Relative quantification of prolactin receptor gene expression in duodenum was determined by quantitative real time PCR.
Results
PRL concentrations were significantly higher in Group P, compared to C1 (181.80 ± 29.65 vs 105.38 ± 28.34; $P < 0.001$). Significantly increased PRL levels in M3 compared to age matched control, confirmed the state of medicamentous HP (182.03 ± 57.80 vs 105.38 ± 28.34; $P < 0.001$). There was no significant difference in PRL concentration between experimental Groups P and M3. Ratio between relative gene expression of PRLR in Groups P and C1 (log2 (P/C1) 10.02 ± 1.41) was significantly higher in comparison with ratio between relative gene expression of PRLR in Groups M3 and C1 (log2 (M3/C1) 4.26 ± 0.60) ($P < 0.001$).
Conclusions
Significantly decreased PRLR gene expression in duodenum could be underlying reason for decreased intestinal calcium absorption in medicamentous HP. In order to maintain calcium homeostasis, when duodenal absorption is compromised, PRL in medicamentous HP will seek for another target organ, such as skeletal system, causing more detrimental effects on bone metabolism comparing to physiological HP.

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P829

Prothymosin alpha and Ki-67 expression in pituitary adenomas

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Introduction
As observed clinically, the development of pituitary tumours and the probability of their recurrence after neurosurgery tend to be unpredictable. The aim of this work was to evaluate Ki-67 and nuclear and plasmatic prothymosin alpha indices as potential pathological markers to predict the aggressiveness of pituitary adenomas.
Material and methods
Ki-67 and prothymosin alpha indices were determined by immunochemistry in specimens excised from neurosurgically removed pituitary tumours. Histopathological material was examined from 30 patients with pituitary macroadenoma (17 females and 13 males, mean age 58.5 ± 12.5 years.) who underwent pituitary tumour surgery. The median value of maximum diameters of tumours was 25.0 mm (IQR 10.25).
Results
Expression of Ki-67, nuclear prothymosin alpha and plasma prothymosin alpha was revealed only in cells of pituitary tumours (being absent in extra-tumoural tissue) and was present in 80, 80 and 90% of adenomas, respectively. The median values of Ki-67, nuclear prothymosin alpha and plasma prothymosin alpha indices were 1.95% (IQR 2.7) 0.63% (IQR 3.5) and 26.4% (IQR 56.6) respectively. The indices of Ki-67 and prothymosin alpha (nuclear and plasma) were not significantly different in adenomas with positive anterior pituitary hormone expression ($n = 20$) as compared with adenomas with negative anterior pituitary hormone expression ($n = 10$). Neither Ki-67 nor prothymosin alpha (nuclear and plasma) indices were found to be significantly correlated with tumour size or patient age. We found no correlation of any of the above-mentioned indices with expression of pituitary hormones in the examined specimens.
Conclusion
Expression of Ki-67 and prothymosin alpha was stated in the majority of pituitary adenomas. Ki-67 and prothymosin alpha, as determined in pituitary tumour specimens, was not related to tumour size nor to the type of pituitary hormone expression.

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P830

Dopamine receptor type 2 (dopamine receptor type 2) inhibits non-functioning human pituitary tumor-derived cell line HP75 migration through ROCK-mediated cofilin inactivation

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Neurosurgery is the treatment of choice of non-functioning pituitary tumors (NFPAs), but its success is strongly affected by local invasion. Medical therapy is still under debate, although the use of cabergoline results in tumor shrinkage in a subset of patients. We recently demonstrated that dopamine receptor DRD2 agonist BIM53097 exerts cytostatic and cytotoxic effects in cultured cells from NFPAs, but no data are present in literature about DRD2 mediated effects on pituitary cell migration and invasion.
A key protein involved in cell migration and invasion is the actin binding protein cofilin, whose activity is negatively regulated by phoshorylation at Ser3 by LIM kinases (LIMK), and LIMK is upstream regulated by ROCK.
The aim of this study was to evaluate the effect of BIM53097 on migration and invasion of the non-functioning human pituitary tumor-derived cell line HP75, and to investigate the molecular mechanism involved focusing on the role of cofilin.
To test cell migration, we performed wound healing assays and images taken immediately and 24 h after scratch were analyzed with image analysis software. Our data demonstrated that 1 μM BIM53097 incubation reduced HP75 cell migration (54% migration vs 65% in control cells, expressed as a % reduction of the free area at 24 h vs 0 h, $P<0.05$ vs control).
Western blot analysis revealed that BIM53097 treatment induced a 2.4-fold increase cofilin phoshorylation, this effect being reversed by ROCK inhibitor, Y27632.
To evaluate the role of cofilin phosphorylation on cell migration, we used phospho-mimiking or phospho-deficient mutants of cofilin (S3D or S3A, respectively). We observed decrease or increase in S3D or S3A expressing cell migration, respectively (9 and 42% respectively, vs 29% migration of mock transfected cells).
In conclusion, our data showed that DRD2 agonist reduced HP75 cells migration through a molecular mechanism that involves the ROCK-dependent phosphorylation of cofilin.

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P831

Functional characterization of a new deletion in CDKN1B 5′-UTR region

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Introduction
CDKN1B gene, which encodes a cyclin-dependent kinase (Cdk) inhibitor, regulates the progression throughout G1 to S cell cycle progression. CDKN1B loss-of-function germinal mutations cause the multiple endocrine neoplasia type 4 syndrome (MEN4).
Objective
The aim of the study is the functional characterization of a new 4 bp deletion in CDKN1B 5′-UTR region, identified in an acromegalic patient.
Materials and methods
We assessed a functional *in vitro* study, based on firefly luciferase reporter gene, on the deleted promoter of human (MCF-7), murine (AtT20/D16V-F2) and rat (GH3) cell lines. Total mRNA and proteins were extracted from peripheral blood of the patient and control subjects to analyze CDKN1B/$p27^{Kip1}$ expression. In addition, we evaluated $p27^{Kip1}$ expression in tissue sections of the patient's GH-secreting pituitary adenoma by immunohistochemistry.
Results
A novel heterozygous deletion in CDKN1B 5′-UTR region was identified in an acromegalic patient. The deletion extends from nucleotide −29 to −26 from the translation start site. Transcriptional activity of the deleted promoter is significantly decreased (~30–60% $P<0.01$). CDKN1B/$p27^{Kip1}$ expression analysis of patient's circulating leukocytes showed a significant reduction (~72%) in mRNA levels, while $p27^{Kip1}$ protein levels are similar to WT controls. Immunohistochemistry shows a reduced $p27^{Kip1}$ expression in the patient's pituitary adenoma compared to the control.
Conclusions
Our data show that the identified deletion causes a significant reduction in promoter transcriptional activity and in CDKN1B mRNA expression, indicating a putative role of the deletion in the patient's disease. Further studies are needed order to understand whether the deletion could impact protein function.

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P832

Correlation of coexpression of pituitary genes in QPCR and microarray study in pituitary adenomas

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Introduction
Mechanism of pathogenesis of pituitary adenomas is still unknown. Gene expression differences in pituitary cells of different origin are not extensively described. Identification of genes specific for pituitary adenomas should enable better understanding of differences in their response to therapy, especially to radiotherapy.
Aim
The aim of our study was to evaluate the correlation of coexpression of distinct pituitary adenoma genes based on QPCR and microarray study.
Material and methods
Analysis of gene expression was performed by QPCR in 76 pituitary adenomas, 25 functioning and 51 nonfunctioning ones. Expression of the examined genes was normalized to the reference index, obtained by calculation of geometric mean of reference genes expression: *GUS-B*, *B2M*, *ACTB*, *EIF3S10*, *UBE2D2,* and *ATP6V1E.*
Microarray study was performed with Illumina HumanRef-8 v3 microarrays (Illumina, Inc.) in 48 pituitary adenomas: 36 functioning (GH, PRL, and TSH) and 12 nonfunctioning ones ('0'). Microarray analysis was performed by BRBArrayTools and R-Bioconductor.
Results
During the assessment of significant correlation between QPCR and microarray results for PRL and GH gene ($R=0.93$; $R=0.94$ $P<0.001$) an unexpected clustering of adenoma subtypes was noticed.
As expected, the highest level of expression for PRL gene was observed in prolactinomas and for GH gene in somatotropinomas respectively. GH expression was 100× higher in somatotropinomas than prolactinomas. When we compared QPCR and microarray results we observed that GH gene was virtually absent in '0' adenomas. Expression of PRL gene was seen in somatotropinomas (4.2× lower in comparison to PRLomas).
Conclusions
The differences in gene expression profiles between pituitary adenomas are confirmed. However, the assessment using simultaneously QPCR and microarrays allowed to separate different subtypes of adenomas.

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P833

Germline aryl hydrocarbon receptor interacting protein (AIP) gene mutations in patients with apparently sporadic pituitary macroadenomas (PMA): initial results

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Germline AIP gene mutations have been linked with familial isolated pituitary adenomas (FIPA). Inactivating mutations of AIP have also been reported in seemingly sporadic pituitary adenomas, particularly of early onset, aggressive, and GH secreting.
Aim
To assess the frequency and type of germline AIP gene mutations in patients with apparently sporadic PMAs.
Material
The study included 31 consecutive patients with pituitary macroadenoma (17 males, 14 females; median age at diagnosis 43 years), followed in the Outpatient Clinic of the Endocricology Department, University Hospital in Krakow. 13 subjects have been diagnosed with non-functioning pituitary adenoma (NFPA), ten – acromegaly, four – prolactinoma, two – Cushing's disease, one – TSH-oma, and one with gonadotropinoma. Median tumor size at diagnosis was 30 mm.
Methods
DNA of all participants was isolated from whole peripheral blood. The six exons of the AIP gene were sequenced using sanger sequencing (ABI 3500). Sequences were compared to reference data at NCBI, accordingly: NM_003977.2 and NP_003968.2. Nucleotide conservativity was estimated by PhyoP. The mutation influence on protein was estimated by PROVEAN protein.
Results
Two patients (9.8%) have been suggested to harbor a germline missense mutation in exon 3 of the AIP gene c.[377A>T];[=], p.[Q126L]; [=] (patient 1 – a 53 year old female with suprasellar NFPA, harboring also SNP rs2276020/c.516>t/p.Asp= in exon 4–5; patient 2 – a 41 year old female with 17 mm ACTH-secreting macroadenoma). The mutation, to our knowledge so far unreported, is localized in a highly conservative region of the gene and most probably leads to abnormal function of AIP suppressor gene.
Conclusions
As both mutation carriers would not be selected for AIP gene sequencing based on clinical features, it seems feasible to search for germline AIP gene mutations in every patient with PMA. The presented report is an initial one, the recruitment of patients is still pending.

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P834

Expression of peroxisome-proliferator activated receptor α in pituitary tumours

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Peroxisome-proliferator activated receptors (PPARs) are involved in a number of neoplasia. PPARα (PPARα) is a partner of the aryl hydrocarbon receptor interacting protein (AIP), which is involved in the pathogenesis of pituitary adenomas (PA). We wished to investigate the potential expression and biological significance of PPARα in PA, especially in GH/PRL-secreting tumours.
Material and methods
A large series of PA was collected ($n=110$, 41 GH-, 14 PRL- and 55 non-functioning PA). PPARα expression was studied by semi-quantitative real-time PCR (qRT-PCR) in 84 PA and/or by semi-quantitative IHC in 74 PA, both of them being performed in 48 cases. PPARα IHC score was obtained by adding nuclear and cytoplasmic scores (range 0–6). Three normal post-mortem pituitaries (NP) were used as controls. The effect of fenofibrate on cell proliferation was studied in GH3 and MMQ cells.
Results
Data from qRT-PCR analysis suggested a down-regulation of PPARα mRNA in 28/84 PA (33.3%) as compared to NP. Overall, PPARα: βactin ratio were very low, with no significant difference between GH/PRL- and NFPA. However, significant PPARα immunoreactivity (score ≥ 2) was more frequently observed in GH/PRL- than in NFPA (82 vs 54.3%, $P=0.009$), resulting in a significantly higher score in GH/PRL-PA ($P=0.0056$ vs NFPA). The highest percentage of PPARα immunopositive nuclei was observed in PRLomas, followed by GH-secreting and NFPA (median 37, 25 and 18% respectively, $P=0.08$). No clear relationship could be observed between PPARα expression and tumour aggressiveness. *In vitro* treatment with fenofibrate (10–100 μM) induced a dose-dependent decrease in cell proliferation in GH3 cells but had no effect on MMQ cells, despite similar levels of PPARα protein were observed by western blot analysis.
Conclusion
PPARα is commonly expressed by PA, especially by GH/PRL-PA. The potential implications of such findings in terms of PA tumorigenesis and treatment should be further investigated.

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P835

AIP expression in non-functioning pituitary adenomas is strongly associated with the gonadotroph phenotype but not with tumour aggressiveness

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The aryl hydrocarbon receptor interacting protein gene has been mainly involved in the pathogenesis of GH/PRL-secreting pituitary adenomas (PA). We wished to study the significance of AIP expression in clinically non-functioning PA (NFPA).
Material and methods
48 NFPA -27 gonadotroph (GnPA), 21 null cell (ncPA) – were studied for AIP, βFSH and cyclin D1 expression by real-time RT-PCR (qRT), compared with four normal post-mortem pituitaries (NP). 36 (21 GnPA, 15 NC) were also studied by semi-quantitative immunohistochemistry (AIP-IHC score: 0–6). Median values are given and data were analysed by non-parametric statistical analysis.
Results
Data from qRT-PCR in NFPA suggested AIP overexpression in 15/27 GnPA (55.5%) vs 2/21 ncPA (9.5%) and underexpression in 1/27 GnPA (3.7%) vs 4/21 ncPA (19%), respectively ($P=0.00028$). The AIP: βactin ratio was significantly higher in GnPA than in ncPA (6.7 vs 2.6, $P=0.0008$), with a strong linear correlation between AIP: βactin and βFSH: βactin ratios ($R=0.49$, $P=0.0004$). The AIP-IHC score significantly correlated with AIP gene expression ($P=0.010$) and was significantly higher in GnPA than in ncPA (3 vs 2, $P=0.027$). No significant correlation was found between AIP expression and tumour invasiveness. However, the AIP: βactin ratio was significantly lower in NFPA with a huge suprasellar extension (SSE grade C/D) or a high Ki67 index ($\geq 3\%$) (2.33 vs 4.23 for SSE, $P=0.042$ and 2.49 vs 6.38 for Ki67, $P=0.0165$), suggesting that AIP is not involved in tumour aggressiveness. Data from qRT-PCR suggested overexpression of CyclinD1 in most NFPA (88.5% GnPA, 78.9% ncPA), although the CyclinD1: βactin ratio was lower in the presence of a high Ki67 index (17.8 vs 1.6, $P=0.037$). A significant linear correlation was observed between AIP and CyclinD1 expression ($R=0.47$, $P=0.001$), especially in GnPA ($R=0.52$, $P=0.006$).
Conclusion
AIP expression in NFPA is strongly associated with the gonadotroph phenotype and may be induced by extracellular factors driving CyclinD1 overexpression.

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P836

Survivin expression in invasive pituitary gland adenomas with a diameter exceeding 20 mm

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Introduction
Survivin is a multifunctional protein and acts as an inhibitor of apoptosis. Its expression occurs in nearly all human cancers. In some tumors survivin expression correlates with the malignant behavior and diminished response to cytotoxic therapy. Data concerning survivin expression in invasive pituitary gland adenomas are contradictory.
Patients and methods
Survivin expression was assessed in 38 invasive pituitary gland adenomas (31 non-functioning tumours, seven somatotroph adenomas) with a diameter exceeding 20 mm, removed during transsphenoidal surgery. 12 control samples of normal pituitary tissue were obtained post-mortem. Tumour size was assessed by preoperative MRI scan. Amplification of survivin gene using sequence specific primers and qRT-PCR method was performed.
Results
The mean age of patients was 54 ± 14 years. The mean tumour size was 33.8 mm $\pm$ 7.8 mm (Min. 20 mm, and Max. 55 mm). Survivin expression was found in 31 out of 38 tumours and in ten out of 12 control samples. There was no difference between the level of survivin expression in pituitary adenomas and in normal pituitary tissue samples.
Conclusions
Survivin expression in invasive pituitary adenomas varies greatly. Our results suggest that survivin expression in invasive pituitary adenomas is comparable to healthy tissue. Since considerable effort has been made in recent years to explore new therapeutic options based on survivin counteracting chemicals, its potential role in pituitary adenomas needs further evaluation.

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Pituitary – Clinical (*Generously supported by IPSEN*)

P837

Evolution of the glucidic metabolism disorders in the acromegalia

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Introduction
Acromegalia is frequently associated to a glucidic metabolic disorders. Hyperinsulinemia and insulin resistance play an important part in the cardiovascular risk and the surmortality of this pathology.
Aim
Study of changes in carbohydrate disorders after cure of acromegalia.
Materials and Methods
This is a retrospective study of 36 patients (16 men and 12 women) hospitalized between 1985 and 2013. Pituitary macro adenoma was found in 27 cases. The seniority of the disease is 07 years (2–15 years). Average age: 42 years (12–68 years). Rate of GH is 218 mUI/l (3–750). All patients were reassessed on the hormonal level and carbohydrate level: IGF1, OGTT/GH, plasma glucose before and after surgery.
Results
Prediabetes was found in 36.1% of cases and diabetes mellitus in 42%. One diabetes mellitus curing after pituitary necrosis and three after stabilization of the disease 5/12 treated by insulin switched to oral treatment and half of patients with prediabetes were curing.
Conclusion
The GH reduce the insulin sensitivity and increase the neoglucogenas and the hepatic glycogenolyse. 1/3 of the patients with diabetes cured after guerison of acromegalia – the diabetes mellitus appear and remains more frequently in aged subjects, having a family predisposition of diabetes and in the patients with a long history of hypersomatotropism.

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P838

Clinical features and therapeutic outcomes of acromegaly during the recent 5 years: single centre experience

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Introduction
The purpose of this study was to characterize management and outcomes of patients with acromegaly seen in single centre in Lithuania.
Methods
The study involved retrospective data collection from charts of 44 patients who were admitted to the centre between 2007 and 2012.
Results
All cases except one were caused by pituitary adenomas (61.4% macroadenomas, and 29.5% microadenomas). The most common co-morbidities were nodular thyroid disease (86.4%), hypertension (86.4%), and IGT or type 2 DM (45.5%). Transsphenoidal operation was applied as the first-line therapy in 65.9% of patients and led to disease remission in 48.3%. Primary medical therapy was administered in 25.0% of cases. Of surgically treated patients, 51.7% were diagnosed with desease recurrence and received medical therapy with somatostatin analogs, cabergoline or bromocriptine. Radiotherapy as a third-line treatment was applied in the 17.2% of patients. Based on the latest GH and IGF1 results, the outcomes were: 38.1% controlled, 28.6% partially controlled, and 33.3% uncontrolled. Control and partial control were achieved in 18.2 and 27.3% of cases in primary medical therapy group, and in 13.3 and 40.0% of cases in combined therapy group. Mean observational period IGF1 in the primary medical treatment group (672.8 ± 206.4 μg/l) was not statistically different from combined treatment group (556.4 ± 259.4 μg/l, $P = 0.139$). We observed stronger correlation of IGF1 and GH in samples taken without medical therapy ($r_s = 0.667$) than in those taken while on SSA treatment ($r_s = 0.416$). GH, gender and age, but not SSA treatment, were significant determinants of IGF1 level in regression analysis.
Conclusions
Control of the disease remains a challenge despite availability of transsphenoidal surgery, SSA, dopamine agonists and conventional radiotherapy. The influence of SSA on IGF1 level remains to be further studied.

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P839

Thyrotropinoma: one tumour, two different clinical presentations

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Thyrotropin-secreting pituitary tumors are $<1\%$ of pituitary adenomas. Clinical manifestations are similar to other forms of hyperthyroidism. Most of them are diagnosed as macroadenoma (microadenomas $<10\%$).
Case 1
A 48 years old woman with menopause presented 6 years ago, consulting in 2009 for weight loss and palpitations. She had elastic goiter and distal tremor. Blood test: TSH 8.66 μUI/ml (0.2–4.2), FT_4 4.7 ng/dl (0.7–1.55), FT_3 10 pg/ml (2–4), α-TSH 5.2 UI/l (0.02–0.9), negative antithyroid antibodies, FSH 10.2 mUI/ml, LH 4.7 mUI/ml, estradiol 28 pg/ml and the rest of pituitary hormones in normal range. Pituitary MRI: macroadenoma (2 cm) with suprasellar invasion, contacting optic chiasm. Campimetry: normal. Treatment was started: propanolol 30 mg/day and octreotide 20 mg/28 days. Six months after: clinical improvement and restoration of menstruation, TSH 0.93, FT_4 1.22, α-TSH 0.42 and slight decrease in tumour size, respecting the optic chiasm (MRI). Transsphenoidal surgery performed (April 2010) and immunohistochemistry was positive to TSH–GH. Immediate postoperative results: TSH 0.04, FT_4 1.1. After 8 weeks: panhypopituitarism (TSH 1.6, FT_4 0.6, α-TSH 0.2). After 6 months, patient is stable with sustitutive treatment and there's no tumour in MRI.
Case 2
A 49 years old woman with history of complete hysterectomy, consulting in 2008 for TSH 8, FT_4 2.99 and positive antithyroid antibodies in a blood test. She presented irritability and irregular goiter. Pituitary MRI: microadenoma (0.6 cm). α-TSH 3.2. She started octeotride 20 mg/28 days. After 6 months TSH 1.7, FT_4 1.08 and pituitary lesson was stable. Transsphenoidal surgery (2011) with immunohistochemistry positive to TSH. 8 weeks postsurgery: TSH 2.3, T_4 0.88, α-TSH 0.34. 6 months after, thyroid axis is normal and there's no tumour in MRI.
Conclusions
We present two different clinical forms of this tumor type, at initial diagnosis and in their postoperative evolution, probably related to tumor size.

However in both cases we observed clinical and analytical response to early medical treatment with somatostatin analogues.

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P840

TSH-secreting pituitary adenomas: a rare cause of hyperthyroidism

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TSH-secreting pituitary tumors (TSH-omas) are a rare cause of hyperthyroidism and account for $<$ 1% of all pituitary adenomas. They are usually benign adenomas arising from a monoclonal expansion of neoplastic thyrotropes.
We report two patients' cases with thyrotropinoma.
The first case is a 73-year-old woman, who presents a TSH-secreting pituitary adenoma in the setting of multiple endocrine neoplasia syndrome type 1 (TSH-omas and primary hyperparathyroidism). The patient had clinical thyrotoxicosis, diffuse goiter, elevated circulating levels of free tri-iodothyronine (FT_3) and free thyroxin (FT_4), and a non-suppressed basal serum TSH (TSH $=$6.53 μU/ml).
Magnetic resonance imaging (MRI) scan showed an invasive pituitary adenoma causing right cavernous sinus invasion compression, there was no evidence of optic chiasmal compression or stalk deviation. The tumor was diagnosed and treated at a late stage (8 years after the onset of hyperthyroidism). Because of comorbidities and the poor general condition in our patient's case, surgical approach of the TSH-oma was contraindicated and pituitary radiotherapy was considered.
The second case is about a 46-year-old woman presented with symptoms of acromegaly and thyrotoxicosis. A large macroadenoma of the pituitary gland was diagnosed by magnetic resonance imaging (MRI) scan. Peripheral thyroid hormone was elevated but TSH remained in the normal range (TSH$=$ 3.2 μUI/ml). GH levels were elevated and remained high after oral glucose tolerance test.
GH/TSH – secreting pituitary tumor (TSH and GH-oma) was diagnosed and transsphenoidal adenomectomy was performed.
We report two new cases of TSH secreting pituitary adenomas. The first patient had a TSH-secreting pituitary adenoma in the setting of multiple endocrine neoplasia syndrome. The second case is particular by its association with an acromegaly.

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P841

Demographical and clinical characteristics of 62 acromegalic patients

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Background
Acromegaly is a relatively rare endocrine disorder which may result in morbidity and mortality. In this study, we report the demographical and clinical characteristics of 62 acromegalic patients who were followed-up at our Department of Endocrinology Clinic.
Methods and results
In this retro-prospective study, medical files of the patients who were followed-up from 1984 to 2013 were examined. Data was obtained for age at the time of diagnosis, gender, time period to the initial diagnosis, follow-up period, levels of GH and IGF1, hyperprolactinemia, tumor size, treatment methods. SPSS-19 version was used for statistical analysis.
There were 62 patients (30 males and 32 females). Mean age at the time of diagnosis was 38.81$\pm$1.4 and mean period to diagnosis 4.5$\pm$0.3 years. Microadenoma was detected in 8 (12.9%) and macroadenoma in 53 (85.5%) of the patients. Tumor sizes were $<$10 mm in 8 (12.5%), 10–20 mm in 16 (25.8%) and $>$20 mm in 31 (50%). GH levels were significantly correlated with the initial tumor size (P=0.002). Initial GH levels were $>$2.5 ng/ml; mean of IGF1 levels was found 993.5$\pm$79. Fifty patients were examined for visual field and 16 (%32) were found to be defective. The surgical method and the tumor size did not show significant correlation (P=0.079). Twenty-seven (43.5%) patients were operated transsphenoidally, 20 (32.3%) patients transcranially. Forty (64.5%) patients were operated once, 7 (11.3%) twice, 2 (3.2%) three times, 1(1.7%) seven times. Thirteen (21%) patients had hyperprolactinemia. Most common symptoms were growth of hands and feet with the facial signs (75.8%). Diabetes mellitus was present in 22 (35%) patients, hypertension in 13 (20.9%), carpal tunnel syndrome in 2 (3.2%). Five (8.1%) patients had conventional radiotherapy. Gamma-knife radiotherapy was applied to 15 (24%) patients. Primary pharmacotherapy was given to 6 (9.6%) patients. Ocreotid LAR was initiated to 52 (84%) patients and lanreotid to 5 (8%) patients during follow-up period after surgery.
Conclusion
Since the diagnosis of our patients were late, the rates of macroadenoma, GH levels, IGF1 levels, visual defect and diabetes mellitus were high. Therefore the number of patients who required radiotherapy and pharmacotherapy post-operatively was high as well. The most important reason of this is that the diagnosis of acromegaly is not considered before the beginning of the clinical symptoms and findings and the consequent late diagnosis.

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P842

Clinical evaluation of follow-up of 62 patients: do treatment methods in acromegaly affect the rates of cure and hypophyseal insufficiency?

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Background
Transsphenoidal surgery of pituitary adenoma is often first-line therapy for patients with acromegaly. Pharmacotherapy and/or radiotherapy are applied when surgery fails to achieve good disease control, or when surgery is impossible or contraindicated. In this study, we report the results of therapies, rates of cure and hypophyseal insufficiency in our acromegalic patients.
Methods and results
Medical files of the 62 patients who were followed from 1984 to 2013. SPSS-19 version was used for statistical analysis. Descriptive and χ^2 tests were used, and results expressed as mean$\pm$S.E.M. Microadenoma was detected in 8 (12.9%) and macroadenoma in 53 (85.5%) of the patients. Among the transsphenoidally operated 27 (43.5%) patients, 4 (14.8%) had postoperative remission, 10 (37%) developed with one or more hormonal defficiency, 1 (3.3%) developed diabetes insipidus. Among the transcranially operated 20 (32.3%) patients, 2 (10%) were postoperatively cured, 17 (85%) developed hypophyseal insufficiency; none of them developed diabetes insipidus. Four patients were operated transcranially due to recurrence after transsphenoidal operation; one of them developed hypothyroidism.
During the postoperatif follow-up, 5 (8.1%) patients had conventional radio-therapy; among whom one patient had remission and one had empty sella. Gamma-knife radiotherapy was applied to 15 (24%) patients; among whom one had remission and three had empty sella; eight of these 15 patients had residue; seven of these eight patients had medical therapy. Two of these 15 patients had residue and hypophyseal insufficiency, one of these 15 patients had recurrence. In addition to six patients with are after surgical therapy, four patients had cure after radiotherapy and/or pharmacotherapy (complet cure in 10 (16%) patients).
Thirty (61.5%) of 52 patients treated with ocreotid had GH levels below 2.5 ng/ml and IGF1 levels within the normal range (for age and gender). Two (40%) of five patients treated with lanreotid had GH levels below 2.5 ng/ml and IGF1 levels within the normal range. In assesment of all the patients, 23 (37.1%) patients GH levels above 2.5 ng/ml, 38 (58.1%) patients had GH levels below 2.5 ng/ml. Initially, diabetes mellitus was present in 22 (35%) patients, in the last follow-up was reduced number of diabetic patients (18 (29%)).
Conclusion
Our success rate in acromegaly treatment has been found to be lower than the literature. We think that early diagnosis, experienced hypophyseal surgeons and further development with regard to medical therapy are required.

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P843

Improvement of quality of life in acromegalic patients evaluated by AcroQoL in Korea

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AcroQoL is a very well-authenticated survey questionnaire capable of evaluating the quality of life (QoL) in acromegalic patients. This study was designed to investigate how AcroQoL of acromegalic patients in Korea would change after medical treatment with octreotide LAR. A total of 58 drug-naïve patients from 11 tertiary centers in Korea were included; all of them were prescribed with octreotide LAR 20 mg at the time of enrollment, and their QoL were evaluated

with AcroQoL survey questionnaires. The observation period was 24 weeks; measurement of GH/IGF1 and AcroQoL survery were performed at baseline, week 12 and 24. With their mean age of 47.2 years (29 males), GH and IGF1 significantly decreased during the first 12 weeks (GH: 4.8 vs 1.9 μg/l, $P < 0.001$ and IGF1: 497 vs 265 μg/l, $P < 0.001$). It was only AcroQoL scores of the psychological appearance subdomain that showed significant increment during the entire 24 weeks (68.6 → 73.5 → 75.4%, $P < 0.05$). The change of AcroQoL scores (psychological appearance subdomain) demonstrated the significantly negative correlation with the change of IGF1 levels ($r = -0.282$, $P = 0.039$). When all of the patients were divided into two groups according to their disease activity at week 24 (controlled vs uncontrolled), AcroQoL scores for psychological appearance subdomain of two groups appeared to change differently over the entire 24 weeks ($P = 0.047$). In conclusion, medical treatment using octreotide LAR resulted in the improvement of psychological aspect of AcroQoL, especially appearance subdomain.

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P844

Enormous, LH secreting gonadotroph adenoma in a male patient

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Introduction

Gonadotrophin-producing pituitary adenomas are usually non-functioning masses, and are not associated with elevated serum gonadotrophins. Functioning LH-producing gonadotroph pituitary adenomas are exceedingly rare in males, causing elevation of serum testosterone.

Case report

We present an adult male who has been admitted to the emergency department a comatose state. Brain MRI revealed a large, lobulated mass of 6 cm caudal and 7.8 cm latero-lateral diameter. The tumor extended from the hypophyseal fossa to the suprasellar cistern, into the ventricular system compressing and dislocating the optic chiasm, causing bitemporal hemianopsia. The mass projected bilaterally to the cavernous sinus without compression of the internal carotid arteries. Ventriculoperitoneal shunting was carried out to relief symptoms. Biopsy of the tumor was obtained and the pathologic analysis confirmed gonadotroph pituitary adenoma with total expression of LH β-subunit, synaptophysin and chromogranin and intense expression of cytokines 8.18, AF1, AF3 and Ki-67 <1%. Hormonal profile showed: PRL 12 ng/ml (2.5–17), LH 11 mIU/ml (0.8–7.6), FSH 4 mIU/ml (0.7–11.1), testo 826 ng/dl (250–840), SHBG 47 nmol/l (18–114), TSH 0.074 IU/ml (0.4–46 m), FT_4 0.52 ng/dl (0.8–2), FT_3 2.92 pg/ml (1.8–4.6), GH 0.05 ng/ml (0.06–5), IGF1 103 ng/ml (94–252), and ACTH 1 pg/ml (7–50) while SST for cortisol was 1, 3 and 4 μg/dl at 0, 30, and 60 min respectively. Extensive tumor excision was achieved through both left pterional and transnasal, transsphenoidal approach. The patient received replacement therapy with hydrocortisone and levothyroxine and was advised for radiotherapy.

Conclusion

Large LH-producing gonadotroph adenomas are rare tumors and sex hormone levels are not always markedly elevated. Gonadotroph macroadenomas are usually treated by surgery and external beam radiation while GnRH antagonists and somatostatin analogues have been used in order to shrink tumor size.

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P845

NFPA and hypopituitarism: a retrospective analysis of 260 patients and focus on the prevalence of isolated hypoadrenalism

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Introduction

Non-functioning pituitary adenomas (NFPA) accounts for about 40% of all pituitary tumors. One or more anteropituitary deficiencies are present at diagnosis in 60–80% of NFPA. Hypopituitarism classically appears with the following order: GH → FSH/LH → TSH → ACTH. Aim of the study was to evaluate the incidence and the order of appearance of pituitary deficiencies in patients with NFPA.

Materials and methods

We retrospectively analyzed the data of 260 NFPA (56% females) followed at our center from 1990 to 2013. At diagnosis all patients underwent a complete evaluation of basal anteropituitary function. Provocative tests for hypotalamic–pituitary–adrenal axis were performed in 234/260. ACTH deficiency was defined by either basal serum cortisol <5 μg/dl, peak of cortisol following ACTH 250 μg stimulation test or insulin tolerance test <18 μg/dl.

Results

At diagnosis, the average age was 50.4±17 years. 63% of patients had a macroadenoma. 50.8% of patients (63% macroadenomas and 29.5% microadenomas) presented at least one anteropituitary deficiency with the following prevalence: 31.6% hypogonadism, 26.7% GH deficiency, 23.9% hypoadrenalism and 13.9% hypothyroidism. In particular, 30% of patients had an isolated deficiency (28% in micro and 30% in macro) and 22% multiple deficiencies (3% in micro and 35% in macro). Isolated deficiencies were represented by hypogonadism in 11.3% of patients (6.7% micro and 14.4% macro), hypoadrenalism in 9.5% (12.3% in micro and 7.6% in macro) and GH deficiency in 8.6% (9.1% in micro and 8.3% in macro).

Conclusions

One-third of patients with a microadenoma had at least one anterior pituitary hormonal deficiency at diagnosis. The presence of patients with isolated hypoadrenalism and hypogonadism suggests that the order of appearance of hypopituitarism does not always follow the one expected. In particular, given the relative high prevalence of isolated hypoadrenalism even in microadenomas, we suggest the full assessment of basal and dynamic anterior pituitary function in all patients with NFPA regardless of tumor size.

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P846

Resolution of severely impaired cognitive function following medical treatment of cystic invasive giant prolactinoma

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Introduction

Giant prolactinomas are rare pituitary tumours. They can present with visual field defect, intracranial pressure symptoms and even temporal lobe epilepsy. Impairment of higher cognitive functions has been reported postoperatively after trans-cranial surgery and following radiotherapy. Reversible cognitive disturbances have been previously reported in patients with surgically decompressed arachnoid cysts but not after medical treatment of giant prolactinoma. We present a case of giant prolactinoma with successful restoration of severely impaired cognitive function with medical treatment alone.

Case report

A 22-year-old university student presented with gradually progressive short memory deterioration over a year and unprecedented poor academic performance. To compensate for it patient started using smartphone messages. Subsequently he was receiving multiple reminders which he could not recall. This unexplained rapid mental decline prompted urgent MRI which showed 48×52×28 mm mixed solid/cystic sellar mass with extrasellar and cavernous sinus extension and chiasmal distortion. Retrospectively he reported erectile dysfunction, but no galactorrhoea. He was hypogonadal with gynaecomastia. His testes were soft ~20 ml. Humphrey's perimetry showed left superior quadrantanopia, visual acuity was normal. Anterior pituitary function revealed hyperprolactinaemia 515.217 mIU/l (0–450), central hypogonadism, normal thyroid, adrenal and somatotroph axes. He was commenced on cabergoline 250 μg/day. Within a week prolactin levels reduced by ~90% (56.061 mIU/l). Three months later MRI showed dramatic tumour shrinkage. Psychometric reassessment showed complete resolution of cognitive dysfunction. Patient has since successfully resumed his master in mathematics course.

Conclusion

Reversible dyscognition with severe short-term memory loss and personality disorders were reported in patients with surgically decompressed extracerebral cysts. Cystic giant prolactinomas can masquerade other intracranial malignancies but surgical intervention should be avoided. Dopamine agonists remains first line treatment obviating risks of pituitary surgery. This case highlights effectiveness of medical management in giant prolactinoma and is the first to report dramatic resolution of debilitating cognitive impairment.

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P847

TSH-secreting pituitary adenoma treated conservatively with cabergoline for more than 10 years

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Background
TSH secreting pituitary adenomas represent small proportion of functional pituitary tumours presenting as hyperthyroidism with elevated thyroid hormone levels and inappropriately normal or increased TSH concentration. They are $\geq$1 cm in size and quite aggressive with tendency to relapse following transphenoidal adenomectomy (TSA). Surgical resection remains gold standard in their definitive treatment while pharmacotherapy with long-acting somatostatin analogues or dopamine agonists has mainly adjunct role in pre-operative restoration of euthyroidism.
Case report
A 44-year-old premenopausal patient presented with mild thyrotoxicosis as repeated thyroid function tests have consistently shown slightly raised free T_3 and free T_4 in the presence of mid-normal TSH. The SHBG was increased by more than 80% above normal range and the α-SU:TSH ratio was equal to 6.4; equilibrium dialysis has excluded the presence of heterophile TSH antibodies. On further investigations she had flat TSH response to TRH test and has failed to suppress TSH to $\leq$0.1 mU/l following liothyronine 20 µg QDS 10 days treatment. The thyroid isotope scan has shown diffusely increased uptake of the thyroid gland; findings were inkeeping with autonomous TSH secretion rather than generalised/pituitary resistance to thyroid hormone or familial dysalbuminaemic hyperthyroxinaemia. Subsequent pituitary MRI has shown calcified pituitary macroadenoma with suprasellar extension, away from the optic chiasm. Considering mild thyrotoxicosis and patient's preference, it was decided to treat her conservatively. She was initially started on cabergoline 1 mg twice weekly; repeated thyroid function tests 4 weeks later were normal. Over the last 10 years she is on cabergoline 500 µg weekly maintenance dose; the TSHoma appearances remains static on serial MRI scans.
Conclusions
Our case illustrates the successful conservative management of TSHoma with relatively low dose of cabergoline. Clinicians are reminded to consider the low cost carbegoline for the conservative management of TSHoma, when treansphenoidal surgery is not a therapeutic option.

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P848

An audit of hyponatraemia in a large UK university teaching hospital

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Background
Hyponatraemia is the most commonly observed electrolyte abnormality in hospitalised patients. The many causes of hyponatraemia may be classified either by volume status or aetiology. Thorough history taking, clinical examination and investigation are necessary in order to accurately determine the cause of hyponatremia and so formulate the most appropriate management plan.
Methods
Patients with serum sodium $<$131 mM were identified by daily automated search of the biochemistry database at Nottingham University Hospitals NHS Trust over a 2 week period (September 2012). Seventy-five patients fulfilled these criteria. Data regarding clinical history, examination of volume status, investigations undertaken, diagnosed aetiology of hyponatraemia, length of hospital stay and treatment were extracted retrospectively from the medical notes using a linked anonymised system.
Results
Patients, 53% female of average age 76.0 ($\pm$13.0), had serum sodium 126.5 mM ($\pm$4.1), potassium 4.4 mM ($\pm$1.0), creatinine 116.8 µM ($\pm$133), plasma osmolarity 270.1 Osmol/kg ($\pm$22.4), urinary osmolarity 362 Osmol/kg ($\pm$141.7) and spot urinary sodium of 38.1 mM ($\pm$40.2). The average length of stay was 18.2 days ($\pm$26.1) and 43% had recorded an examination of volume status. The aetiology of hyponatraemia was established in 37.3% of patients. 11 patients were recorded as having SIADH but in only two of these were investigations sufficient to substantiate this conclusion. The most common aetiological association was malignancy (21%), heart failure (17%), thiazides (16%) and SSRIs (7%).
Conclusions
Hyponatraemia was usually an isolated electrolyte abnormality with normal serum potassium and mild renal impairment and affected a predominantly elderly population necessitating a hospital stay in excess of 2.5 weeks. There was room for improvement in clinical and laboratory investigation. The high prevalence of malignancy was notable and diagnosis of SIADH was particularly poorly substantiated.

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P849

A statistical model of patient satisfaction after surgery for non-functioning macroadenomas of the pituitary gland

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Objective
To provide a latent class regression model predictive of surgical outcome in patients with non-functioning macroadenomas (NFMA) of the pituitary gland.
Patients and methods
Seventy-five patients with surgically treated NFMA of the pituitary gland were analyzed retrospectively. Thirty-two patients were male. Median age at the time of surgery was 58 years (range: 16–84 years). Median follow-up time was 90 months (range: 14–208 months). Gender, age, tumor size, parasellar tumor growth, surgical approach, tumor remnant, tumor recurrence, number of surgical procedures, adjuvant radiotherapy, postoperative course of vision as assessed by an ophthalmologist, and postoperative functioning of the adenohypophysis, each as documented in our patient files, were chosen as potentially predictive covariates. Affection of nasal airways, impairment of vision, neccessity of hormone substitution, dependency on nursing, return to work, quality of life and overall satisfaction with the surgical result, each as recorded in a standardized patient questionnaire at follow-up, were chosen as outcome variables. Multiple latent class models (LCM) were fitted. Covariates with a probability of $<$0.2 to exceed the absolute t value in the respective LCM were considered predictive of class membership. The lowest Bayesian information criterion (BIC) of all LCM was considered indicative of best fit.
Results
The most parsimonious LCM consisted of two classes 'satisfactory outcome' (estimated patient share (EPS): 60.5%; proportion of overall satisfied patients (POSP) in class: 100.0%), and 'potentially unsatisfactory outcome' (EPS: 39.5% and POSP: 73.8%), with age, tumor size, parasellar tumor growth, surgical approach, postoperative course of vision, and postoperative functioning of the adenohypophysis as predictive covariates.
Conclusion
The presented model allows to identify individuals at risk for an unsatisfactory outcome after surgery for NFMA of the pituitary gland.

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P850

Endocrine abnormalities in primary empty sella

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Aim
Empty sella is usually an incidental finding. The term primary empty sella (PES) makes reference to the herniation of the subarachnoid space within the sella turcica in patients with no history of pituitary tumor, surgery or radiotherapy. The aim of this study was to evaluate hormonal abnormalities associated with empty sella.
Materials and methods
Twenty-three primary empty sella patient were retrospectively analyzed. Hormonal evaluation including free thyroid hormones, TSH, GH, IGF1, FSH, LH, cortisol and prolactin was done.
Results
A total of 23 patients diagnosed clinically and biochemically of hormonal abnormalities were found to have empty sella on magnetic resonance imaging. Of the 23 patients, 11 were male (47.8%) and 12 (52.2%) were female. Mean age was 42.22$\pm$17.71 years. Mean age of women was 45.42$\pm$15.25, while men had 38.73$\pm$20.21 mean age. No statistically significant difference was observed between the two groups ($P>0.05$). Ten patients (43.5%) were euthyroid while 13 patients (56.5%) were hypothyroid. Eight patients (34.8%) were detected hypocortisolemic while 15 patients (65.2%) had normal cortisol levels.

Hypogonadism were detected in 16 patients (70%). Hypoprolactinemia was detected in 10.5% in patient, hyperprolactinemia in 26.3% and normal prolactin levels were detected in 63.2% of patients. IGF1 levels were normal in 50% patient. There was negative correlation between age and free T_3 ($P=0.021$; $r=-526$).
Conclusions
Symptoms related to endocrine dysfunction is rare in adult patients developed empty sella. The most prominent features are secondary amenorrhea, loss of libido and symptoms due to the loss of pituitary reserve. In our patients; hypogonadism is the most common hormone deficiency and hypothyroidism and hypocortisolism followed that. Hypothyroidism is increasing as age increases. Care should be taken in this regard.

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P851

What is in the sella while spying on cancer? The role of FDG–PET/CT in differential diagnosis of sellar mass during staging for malignant disease

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Positron emission combined with computed tomography using ^{18}F-deoxy-glucose (FDG–PET/CT) is increasingly used in the staging and detection of malignant disease. Normal pituitary is not visualized by routine FDG–PET/CT and its radiological evaluation relies predominantly on magnetic resonance imaging (MRI). The role of FDG–PET/CT in differential diagnosis of sellar mass, in patients investigated for malignant disease, will be discussed.
Case 1
FDG–PET/CT restaging was requested for 70-year-old male suspected of having hilar lymphadenopathy. In the past he was treated for two malignancies (lung and rectal carcinoma) but FDG uptake was remarkable only in the sellar region. Although MRI confirmed a pituitary mesoadenoma, clinically he was asymptomatic with normal anterior pituitary function and no diabetes insipidus. Immunostaining after trans-sphenoidal pituitary surgery confirmed diagnosis of silent gonadotroph–pituitary adenoma.
Case 2
In a 43-year-old male patient with sudden onset of headache, nausea, fatigue, dizziness and visual loss pituitary MRI disclosed an intra and suprasellar lesion with a narrow waist while on scull X-ray sella appeared normal. Panhypopituitarism without diabetes insipidus, was diagnosed and replaced. Chest X-ray rose the suspicion of a tumor in the right lung, subsequently confirmed by CT. On FDG–PET/CT an avid uptake was detected in the lung and pituitary. After an open biopsy of the lung tumor a microcellular bronchial carcinoma was diagnosed and patient underwent chemotherapy.
In asymptomatic patients undergoing staging for malignant disease, an avid FDG uptake in the sellar region can disclose a pituitary incidentaloma, which can be confirmed by pituitary MRI. In patients with sudden onset of sellar mass symptoms and hypopituitarism (and/or diabetes insipidus), specific pituitary MRI findings may raise the suspicion of metastasis in the pituitary. Therefore, when clinical suspicion of malignancy is present spying on cancer with FDG–PET/CT may have a role in pituitary imaging, detection of primary tumor and distant metastases.

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P852

Lymphocytic hypophysitis: natural history and management in the 21st century

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Introduction
Lymphocytic hypophysitis (LH) is a rare condition that has been increasingly recognised. We studied the natural history and current management of patients with lymphocytic hypophysitis.
Methods
We performed a multi-centre retrospective review of all patients that either had histologically proven disease or a strong clinical suspicion for its presence, diagnosed from 2000 onwards. Cases of secondary hypophysitis or granulomatous or xanthomatous or other mixed forms of primary hypophysitis were excluded.
Results
Of 20 patients included 16 (80%) were females, 18 (90%) were Caucasians and the mean age was 39.5 years. Ten out of 16 (62.5%) females presented either in the antepartum or the *post-partum* period. Headache was the commonest presenting complain (13/20, 65%), followed by visual field impairment (7/20, 35%). Anterior, posterior and combined hypopituitarism was observed in 19/20 (95%), 7/20 (35%) and 6/20 (30%) respectively. Stratification into individual hormone deficiencies showed that ACTH deficiency was the most prevalent affecting 18/20 (90%) patients, followed by TSH, LH/FSH, GH, ADH and prolactin deficiencies. The duration of symptoms prior to a diagnosis had been made ranged for many months to a few years, for at least half the patients. Surgery was peformed in 9/20 (45%) for the following indications: visual field disturbances (6) and severe headache (2). The remaining cases were medically managed. At follow-up there were no fatalities. At 1 year follow-up all (18/18) patients were still requiring ≥ 1 hormone replacement; symptomatology (mainly headaches) persisted in 8/18 (42.1%) and 2/18 (11.1%) of patients had residual visual field defects.
Discussion
We report a pragmatic study of the current practices of LH. We would like to emphasize the favourable prognosis of this condition, but at the same time the high morbidity associated with it; of concern there remains a long delay between the appearance of symptoms and the diagnosis been reached.

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P853

Assessment of the hypothalamus–pituitary–adrenal axis with different corticotropin tests in adult patients with Prader–Willi syndrome

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Introduction
Hypothalamic–pituitary anomalies are well proven in Prader–Willi syndrome (PWS). In this context, it has been previously reported that central adrenal insufficiency (CAI) may be part of the PWS phenotype. However, the diagnostics of CAI is critical and debated, due to the lack of fully reliable tests. Several studies have looked at the clinical usefulness of the low dose (1 μg) short Synacthen test (LDSST) compared to the conventional dose (250 μg) test (SDSST) in patients with pituitary disease. Actually, the dose used in the SDSST is considered supraphysiological and might produce a deceivingly adequate cortisol (*F*) response. Nevertheless, other reports suggested no difference between the LDSST and SDSST in patients with multiple pituitary hormone deficiency.
Objective
To compare the F response to both LDSST and SDSST in a large group of PWS adults.
Methods and patients
Forty-six PWS subjects, 23 males, aged 18–41 years, underwent LDSST and SDSST. In each test blood samples for F determination were taken at 0 and 30 min. A *F* peak >18.1 μg/dl was considered to be a normal response.
Results
The mean peaks of *F* after LDSST and SDSST were 22.2 ± 0.7 μg/dl (mean $\pm$ S.E.) and 22.7 ± 0.7 μg/dl respectively ($P=0.8$). The average increase of F from baseline was 10.4 ± 0.7 μg/dl (LDSST) and 12.1 ± 0.7 μg/dl (SDSST) ($P=0.02$). The LDSST and SDSST produced 32 normal and two abnormal concordant results. Seven patients who passed the SDSST failed the LDSSD, while five subjects failed the SDSST but passed the LDSSD.
Conclusions
F responses to different SSTs were discordant in 26.1% of our cases. In this light, further research is needed to identify the more reliable test for diagnosing CAI in these patients – e.g. an ITT or overnight metyrapone test on those who had abnormal response to LDSST or SDSST in order to confirm the presence of CAI.

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P854

Mean platelet volume in male hypogonadotropic hypogonadysm: the relationships among with MPv, low testosterone levels, metabolic syndrome, impaired fasting glucose and cardiovascular risk

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Aim
Isolated male hypogonadotropic hypogonadism can be congenital or acquired. Mean platelet volume (MPV), which is a determinant of platelet function, is an independent risk factor for cardiovascular disease. The aim of this study is to evaluate MPV values in untreated, normosmic, isolated, male, idiopatic hypogonadotropic hypogonadism (IHH) patients, and the relationships among MPV, low testosterone levels, metabolic syndrome, impaired fasting glucose (IFG) and cardiovascular risk in these patients
Materials and methods
Thirty-one patients with untreated, normosmic, isolated, male, idiopatic hypogonadotropic hypogonadism (mean age 22.0 ± 4.9 years) and 30 healthy controls (mean age 22.5 ± 7.5 years) who came to Erzurum Regional Education and Research Hospital, Outpatient Clinic of Endocrinology Department were included in the study. Patient group and the control group were matched for age and BMI. It was used the IDF criteria (2005) for diagnosis of metabolic syndrome, and the ADA criteria (2007) for diagnosis of impaired fasting glucose. All hormonal analyses were done by chemiluminesance assay. All the study subjects were evaluated by biochemical and platelet parameters. Hypogonadotropic hypogonadism was defined as total testosterone <229 ng/dl, absent or inadequate as pituitary gonadotropins. Homeostasis model assessment (HOMA–IR) was used as a measure of insulin sensitivity using the equation: Fasting insulin (mU/l) $\times$ fasting glucose (mmol/l)/22.5.
Result
The MPV levels in IHH patients were also significantly higher than controls (8.6 ± 0.65 and 7.6 ± 0.54 fl, respectively; $P=0.0001$). To assess the correlation with MPV, a Pearson correlation analysis was performed on each variable. MPV had a positive correlation between parameters of metabolic syndrome ($r=0.444$; $P=0.0001$), IFG ($r=0.371$; $P=0.04$), insulin ($r=0.820$; $P=0.02$), HOMA–IR ($r=0.822$; $P=0.023$), and BMI ($r=0.373$; $P=0.012$). MPV had a negative correlation between total testosterone ($r=-0.586$; $P=0.0001$), free testosterone ($r=-0.634$; $P=0.0001$), LH ($r=-0.471$; $P=0.0001$), FSH ($r=-0.434$; $P=0.0001$). Metabolic syndrome and IFG in IHH patients had significantly more often than controls ($P=0.003$ and $P=0.0001$, respectively). The multiple regression analysis between MPV and other risk factors was performed. The age, metabolic syndrome, IFG, BMI, insulin, CRP and HOMA–IR were independent predictive factors for high MPV levels.
Conclusion
These results suggest that subjects with male IHH are susceptible to increased platelet activation and increased MPV values which contribute to increased risk of cardiovascular complications. From this study it has been observed that hypogonadotropic hypogonadism with low testosterone may be a feature of the metabolic syndrome, impaired fasting glucose, increased MPV levels, and cardiovascular risk in young adult males. Thus, in IHH patient, testosterone replacement therapy may be useful protecting from the cardiovascular disease. In IHH patients, further study is needed to better understand low testosterone relationship between these three components for preventive from the cardiovascular risk.

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P855

The effects of octreotide acetate long-acting repeatable on mean platelet volume in acromegaly: octreotidelar may have a detrimental effect on MPV, a new indicator of atherosclerosis

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Introduction and objective
Cardiovascular mortality is high in acromegaly. Our aim in this study was to determine the levels of the new cardiovascular marker in active acromegaly patients, the mean platelet volume (MPV) values before and after octreotide acetate long-acting repeatable treatment.
Material and methods
Thirty-six patients with active acromegaly who presented at the Endocrinology Department (mean age 46.0 ± 14.0 years and mean BMI: 30.4 ± 5.1 kg/m^2) and 30 age- and BMI-matched (mean age 46.4 ± 12.5 years and mean BMI: 31.7 ± 8.1 kg/m^2) healthy individuals were included in the study. All complete blood count (CBC) analysis was performed with the automatic hematology analyzer Beckman Coulter LH 750 (Beckman Coulter, USA). The platelet count (PC), MPV, platelet distribution width (PDW) and plateletcrit (PCT) were evaluated. The differences between before and after treatment values were analyzed with the paired *t*-test. The independent *t*-test was used for the comparison of patient and control groups. Relationship between variables was evaluated with Pearson's correlation test. A $P<0.05$ was considered statistically significant.
Results
Serum MPV levels in acromegalic patients were not different from control subjects before treatment (7.9 ± 0.8 and 7.9 ± 0.9 fl respectively). Serum MPV values increased significantly in the acromegalic patients after treatment (8.3 ± 0.9 fl, $P=0.047$) and differed from control subjects. MPV in acromegalic patients showing remission or cure was significantly higher than control subjects after the treatment. No statistically significant differences were found between the other parameters such as hemoglobin, platelet count, WBC count, Hgb, Hct, PCT, and PDW.

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P856

GH replacement therapy during pregnancy in a patient with Sheehan's syndrome

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Introduction
Appropriate replacement therapy of not only gonadotrophins, but other deficient pituitary hormones is important in patients with hypopituitarism for a successful pregnancy. Data regarding GH replacement therapy during pregnancy is limited. We would like to present a case with panhypopituitarism including severe GH deficiency due to Sheehan's syndrome, who achieved successful pregnancy with GH replacement therapy in the first half of pregnancy.
Case
The patient was a 30-year-old woman with Sheehan's syndrome diagnosed 3 years after her last delivery. She had panhypopituitarism and was treated with prednisolone, levothyroxine, combined estrogen–progesterone pills and GH. Since the patient wanted to concieve again, ovulation induction was carried out. Conception occurrred after second trial of ovulation induction. Prednisolone and levothyroxine doses were adjusted according to the trimester of her pregnancy and GH replacement therapy was continued until 20 weeks of gestation and the dose was adjusted according to her IGF1 levels. Normal IGF1 levels were maintained without exogenous GH until birth most likely due to placental GH secretion. The pregnancy and delivery were uneventful and the patient gave birth to a term healthy baby.
Conclusion
The dose of deficient hormones should be adjusted according to trimester of pregnancy in patients with hypopituitarism. GH may be used in selected cases with hypopituitarism to increase the success of fertilization and implantation. GH needs to be discontinued in the second half of pregnancy since placental GH is able maintain normal IGF1 levels.

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P857

Constipation in elderly men, the initial manifestation of empty sella

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An empty sella (ES) develops when cerebrospinal fluid (CSF) compresses pituitary tissue until it lines the sellar floor and walls and lead to shrinkage of pituitary gland. Primary ES occurs when CSF enters the sella from the subarachnoid space that may or may not be associated with increased intracranial pressure. Secondary ES is a result of an injury to the pituitary itself (e.g. pituitary apoplexy) or the consequence of surgical or radiation treatment. Primary ES is

most commonly found in middle-aged women with a history of multipl pregnancies and large majority of those women are asymptomatic, therefore it is discovered as an incidentally. However primary ES in men is seen in older age and it is discovered during the diagnostic evaluation of anterior pituitary deficiency. In this case the elderly man admitted with chronic fatique and constipation was presented.
A 73-year-old man had severe constipation in addition to asthenia and adynamia for over the past 4 years. Even, he was followed in surgery inpatient clinic for constipation mimicking acut abdomen syndrome about 1 year ago. He had no history of head injury or surgery. His physical examination revealed a pale face and a decrease in total body hair. Endoscopic and colonoscopic evaluation of gastrointestinal system was normal. His biochemical values are as follows; fasting glucose level was 74 mg/dl (74–100), serum sodium level was 135 mmol/l (136–145), serum potassium level was 5 mmol/l (3.5–5.1), serum FSH level was 0.99 mIU/l (the range for men 1.4–18.1), LH level was 0.36 mIU/l (range for men 1.7–9.6), cortisol level was 2.29 μg/dl (4.3–22.4), free T_4 level was 0.23 pmol/l (0.89–1.76), TSH level was 2.54 μIU/ml (0.35–4.5). ACTH: 2.7 pg/ml (7.2–63). GH <0.03 ng/ml (0.03–2.47), somatomedin c: 41 ng/ml (94–245). Gadolinium magnetic resonance imaging confirmed empty sella with thin rim of pituitary gland. Glucocorticoid and thyroid hormone replacement therapy was then started. His complaints including constipation and asthenia were recovered during the follow-up and he was feeling much better than before.
Therefore, the presented case suggest that constipation with asthenia and adynamia should be considered as the initial manifestation of ES in elderly man.

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P858

A case of IgG4-related xanthomatous hypophysitis

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Introduction
Hypophysitis is an inflammatory disease of the pituitary that may mimic tumors. Primary hypophysitis has been classified as lymphocytic (LH), granulomatous (GH), and xanthomatous (XH). It has been recently proposed to be an IgG4-related autoimmune disease (serum IgG4 concentration: 135 mg/dl), proven by tissue IgG4 immunostaining.
Case description
A 23-year-old men suffered from typical cluster type headache. Two years after the first symptoms, diabetes insipidus occured. His testosterone level was low with low serum FSH and LH suggesting central hypogonadism, but all the other anterior pituitary hormone levels were normal. Sella MRI scan depicted a 17 mm inhomogenous mass. After the transphenoidal surgery the pituitary tissue was showed by accumulation of foamy cells and *xanthomatous epithelioid cells*. After stopping the preoperative hydrocortisone therapy the headache returned. The endrocrine work up revealed hypadrenia (morning cortisol: 96 nmol/l and ACTH: 3.38 pmol/l), hypothyroidism (ft4: 10.5 pmol/l), hypogonadism (testosterone: 3.44 nmol/l) with FSH: 3.3 mIU/l and LH:2.8 mIU/l. Hydrocortisone, levothyroxine and testosterone were stepwise reintroduced. During the follow-up we could stop hydrocortisone, levothyroxine, whereas he has permanently required desmopressin and testosterone substitution. Occasionally headache attacks occur and dissappeare with glucocorticoid administration. Two years after the initial diagnosis the hypophysitis was proven to be IgG4-related by his tissue IgG4 immunostaining as well as by his elevated serum IgG4 concentration (815 mg/l).
Conclusion
We describe a case of IgG4-related xanthomatous hypophysitis causing cluster type headache permanenty requiring ddAVP (desmopressine) and testosterone supplementation however, without need for maintenance medication with hydrocortisone and levothyroxin. In periods of headaches the patient requires glucocorticoids supporting the possible autoimmune origin of the disease.

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P859

Pituitary abnormalities in short adolescents and young adults with sickle-cell disease and recurrent vaso-occlusive crisis

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Introduction
Growth failure is the most frequent endocrine abnormality observed in patients with sickle-cell disease SCD. Decreased synthesis of IGF1 might be secondary to a disturbed GH–IGF1 axis and defective GH secretion has been reported in some patients. Infarction, atrophy, and hemorrhage may occur in the pituitary gland in SCD during or following the vaso-occlusive crisis.
Objective
To define the possible abnormalities of pituitary gland in SCD we measured the circulating concentrations of IGF1 and studied the magnetic resonance imaging (MRI) of the pituitary gland in seven adolescents and young adults with SCD with short stature (HtSDS <-2) and history of recurrent painful crisis.
Methods
Seven patients with SCD (age: 24.2 ± 4.5 years) and short stature (HtSDS $=2.5\pm0.4$) and history of severe and recurrent vaso-occlusive crisis (at least three in the past 3 years) were studied. All were transfusion-dependent, with full pubertal development (Tanner's stage 5) (euogonadal). They were regularly transfused since early childhood and underwent chelation therapy using desferrioxamine which was replaced by deferasirox for the last 4–5 years.
Results
In the seven patients with SCD circulating IGF1 were decreased (IGF1 SDS $=-2.1\pm0.5$) compared to adults standards. Pituitary MRI showed abnormalities in 4/7 of these patients in the form of heterogeneous appearance of the anterior pituitary, presence of single or multiple hypointense foci due to hemosiderin deposition in the pituitary (4/7) and significantly decreased (2/7) or increased volume (1/7). These lesions can be explained by hemosiderosis of the gland and/or ischemia during the vaso-occlusive crisis.
Conclusions
Pituitary MRI showed significant abnormalities of the anterior pituitary gland in SCD patients with short stature and significant history of vaso-occlusive crisis. This study demonstrated the value of MRI of the pituitary to support investigating of the GH–IGF1 axis in these patients.

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P860

Evolution of glucose tolerance status after treatment of acromegaly: a prospective study in 57 patients

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Background
Acromegaly is frequently associated with impaired glucose tolerance (IGT) or diabetes and treatment has also differential effects on glucose metabolism depending on specific type of medication.
Objective
To study in 57 acromegalic patients evolution of glucose metabolism according to disease activity and treatment.
Methods
IGF1 measurement, oral glucose tolerance test (OGTT) and HOMA test to evaluate insulin sensitivity (HOMA-S) and β-cell function (HOMA-β) were performed in all patients at diagnosis and at last follow-up (median follow-up 7 years).
Results
At diagnosis of acromegaly, 14 patients (25%) were diabetic, 15 (26%) had IGT and 28 (49%) had normal GT. At the last visit, 32% were diabetic and 26% remained glucose intolerant. There was a decrease in fasting glucose (-10.4 mg/dl) in the 20 patients cured by surgery (group I), whereas it increased in the 28 patients controlled under medical therapy (group II, $+5.5$ mg/dl) and in the nine patients with active disease (group III, $+8.8$ mg/dl; $P=0.016$ vs group I). There was no significant difference in evolution of HbA1c and HOMA-S between groups, but loss of β function was more pronounced in groups II ($-74.1\pm12.5\%$) and III ($-38.7\pm6.4\%$) vs group I ($-26.1\pm12.9\%$; mean ± S.E.M.; $P=0.035$). Type of treatment influenced changes in HbA1c between diagnosis and last visit with a decrease (-1.7%) in patients under pegvisomant and an increase in patient treated by somatostatin analogs ($+0.3\%$; $P=0.044$). In the cured patients, 30% had improved their GT status vs only 11% in the other groups, while deterioration was more frequently observed in patients with medical therapy.

Conclusions
This study shows that more than 50% of acromegalic patients have still IGT or diabetes at distance from diagnosis. Improvement of glucose metabolism is mainly observed in cured patients and in patients treated with pegvisomant.

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P861

Serum prolactin in advanced chronic liver disease

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Introduction
Hyperprolactinemia is a frequent endocrine disorder with well known harmful effects on the reproductive system and bone metabolism. Besides prolactinomas several drugs and disorders such as renal failure and hypothyroidism have been shown to cause hyperprolactinemia. Based on former studies liver cirrhosis has also been suggested to cause hyperprolactinemia while mechanisms have not been identified yet. In this study we set out to investigate the prevalence and predictors of hyperprolactinemia in 178 patients with liver cirrhosis of different etiologies.
Results
Eighteen from 178 patients, seven females and 11 males, displayed elevated serum prolactin levels. When patients who took medication or suffered from co-morbidities that are known to potentially cause hyperprolactinemia were excluded, only three males from 55 patients without confounding factors had increased serum prolactin levels. Prolactin levels were similar in patients with liver cirrhosis of different etiologies.
Conclusion
Our data suggest that hyperprolactinemia is not commonly found in patients with liver cirrhosis but is mostly associated with intake of drugs or presence of comorbidites which are known to potentially cause hyperprolactinemia. We thus hypothesize that in contrast to former studies liver cirrhosis is not a common cause of hyperprolactinemia and that in the absence of co-morbidities or drugs that are known to potentially increase prolactin levels marked hyperprolactinemia needs further investigation in patients with liver cirrhosis.

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P862

Assessment the relationship between TSH and selected anthropometric parameters: preliminary report

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Introduction
The majority of secreted hormones influence the whole body, its weigh and constitution as the results of ongoing metabolism. Scientific studies have reported the existence of relationship between the TSH and selected anthropometric parameters such as BMI or body weight.
Aim
The aim of the study was to assess the relationship between the value of TSH and selected anthropometric parameters in the group of endocrine patients.
Materials and methods
The study involved 87 patients with thyroid disorders who were admitted to the Endocrinology Department in 2013. We excluded patients treated with statins and patients with TSH values below 0.35 μIU/ml. Blood samples for TSH concentration were collected from patients in the morning. Anthropometric parameters were measurement in the morning in accordance with generally accepted methodology. The collected data were statistically analyzed, $\alpha = 0.05$.
Results
Mean age was 42.98 ± 15.79 years. The mean concentration of TSH was 2.91 ± 7.82 μIU/ml. The average value of waist circumference was 88.30 ± 17.59 cm hip circumference 104.33 ± 13.62 cm. The average BMI was 27.24 ± 7.35 kg/m^2, WHR 0.84 ± 0.10, and WHtR 53.99 ± 10.59. The average percentage of body fat was $33.00 \pm 10.10\%$, lean body mass 47.59 ± 10.96 kg, and muscle mass 44.71 ± 11.31 kg. The average of the strength of hand was 30.36 ± 9.00 kg. In the preliminary stage of the study we did not find any statistically significant correlation in TSH concentration and waist circumference ($R = 0.16$; $P = 0.1221$), loins circumference ($R = -0{,}02$; $P = 0.8023$), BMI score ($R = 0.04$; $P = 0.6873$), percentage of body fat ($R = 0.01$; $P = 0.8807$), lean body mass ($R = -0.01$; $P = 0.8915$) and muscle mass ($R = -0.02$; $r = 0.8296$). There were observed positive significant correlation between the TSH concentration and WHR index ($R = 0.25$; $p = 0.0160$), and between TSH: WHtR ratio ($R = 0.21$; $P = 0.0420$). In addition the results showed a negative correlation between TSH concentration and the strength of hand ($R = -0.24$; $P = 0.0215$).
Conslusions
The thyroid function (based on screening TSH exam) could affect body constitution and muscle strength. Enlargement of the studied group is necessary to confirm the observation.

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P863

Is pregnancy possible with acromegaly?

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Acromegaly is usually caused by a GH-secreting pituitary adenoma. Although fertility is frequently impaired, pregnancy can be possible due to improvement in diagnosis and treatment modalities. Tumour enlargement and nontumoral lactotroph enlargement related with pregnancy can compress the optic chiasm and cause visual impairment. Optimal management of acromegaly during pregnancy is not well established. In this paper our experience about the clinical, laboratory, radiologic data and maternal–fetal outcomes of our pregnant acromegalic patient is presented. A 38 years old patient had been diagnosed as acromegaly when she was 31 years old. She was operated for a 35×30 mm cystic macroadenoma and followed with somatostatin analogue treatment. 3 years after the operation she became pregnant and octreotide-LAR treatment was halted at 3 months of pregnancy. She was not overweight and she did not have hypertension before pregnancy. After delivery GH levels elevated and octreotide-LAR treatment was restarted and continued throughout lactation. Headache without visual abnormalities developed during pregnancy, but tumour growth could not be demonstrated *postpartum* at imaging of pituitary. She delivered a healthy baby without complications related with acromegaly. The child is 4-year-old now and healthy. It can be concluded that uneventful course of pregnancy and delivery is possible with drug treatment withdrawal in acromegalic patients, but close follow-up is mandatory after delivery, due to recurrent nature of the disease.

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P864

A case of lymphocytic hypophysitis presented as hemorrhagic pituitary macroadenoma

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Introduction
Lymphocytic hypophysitis is an uncommon disease of the pituitary gland mimicking pituitary macroadenoma on magnetic resonance imaging (MRI).
Case
A 37-year-old female admitted to our clinic with headache, amenorrhea, polyuria and history of pituitary microadenoma. On laboratory examinations, prolactin level was mildly elevated (42 ng/ml) and FSH–LH levels were normal (2.4–4.04 mIU/ml) despite the low estrogen level (<20 pg/ml). Water

deprivation test confirmed central diabetes insipidus (DI). Pituitary magnetic resonance imaging revealed an 16 mm hemorrhagic macroadenoma with partial compression over optic chiasma. Patient underwent a transnasal/transphenoidal resection of the mass. Histopathology was suggestive of lymphocytic hypophysitis with diffuse infiltrate of predominantly B lymphocytes. After the surgical approach, her prolactin level was normal but diabetes insipidus and hypogonadotrophic hypogonadism persisted.
Discussion
Differential diagnosis of lymphocytic hypophysitis may be difficult because of its presentation as an expanding pituitary adenoma. Besides hemorrhagic appearance of lymphocytic hypophysitis on pituitary MRI is rarely reported.

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P865

Effect of chronic treatment with cabergoline and testosterone replacement on metabolic parameters in male patients with prolactinomas and hypogonadism

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Hyperprolactinemia is reportedly associated with impaired metabolic profile, particularly in patients with concomitant hypogonadism. The current study aimed at investigating the effects of 12 and 24 month-continuous cabergoline (CAB) treatment on metabolic profile in male hyperprolactinemic patients. Thirty-two men with prolactinomas, including 22 with testosterone $<$ 8 nmol/l (HG, 69%) and 10 with T $>$ 8 nmol/l (non–HG, 31%) entered the study. In all patients, metabolic parameters were assessed at diagnosis and after CAB treatment. Compared to non-HG, at baseline HG patients had higher PRL and waist circumference (WC). Testosterone significantly correlated with BMI. Metabolic syndrome (MetS) prevalence was not significantly different in HG (60%) and non-HG (45.4%). 12-month CAB induced PRL normalization in 91% of patients. HG prevalence significantly decreased (28%) and non-HG prevalence significantly increased (72%). Lipid and anthropometric parameters, as well as fasting insulin (FI), ISI_0, HOMA-beta, HOMA–IR and VAI were all significantly improved compared to baseline. Testosterone was the best predictive factor for FI. Testosterone percent change (Δ) significantly correlated with ΔCholesterol (CHO), ΔWeight and ΔBMI. Compared to non-HG, HG patients had higher weight, BMI, WC and HOMA-β. MetS prevalence did not differ in HG (33%) and non-HG (13%). In HG, testosterone replacement was started. After 24 month-CAB, PRL normalised in 97% of cases. HG prevalence significantly decreased (6%) and non-HG prevalence significantly increased (94%). Lipid and anthropometric parameters, as well as FI, ISI_0, HOMA-beta and HOMA-IR were all significantly improved compared to baseline, with FI, ISI_0, HOMA-beta and HOMA–-IR also significantly ameliorating compared to 1-year evaluation. Compared to non-HG, HG patients still had higher weight, BMI and WC. MetS prevalence did not differ in HG (11%) and non-HG (13%). In conclusion, in hyperprolactinemic hypogonal men proper replacement of testosterone deficiency induces a significant improvement in metabolic profile, even though the amelioration in lipid profile might reflect the direct action of CAB.

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P866

A middle aged woman with isolated ACTH deficiency associated with transient GH deficiency

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Introduction
Isolated ACTH deficiency (IAD) is a rare entity characterized by secondary adrenal insufficiency with low levels of serum cortisol, decreased production of ACTH, adequate secretion of other pituitary hormones and normal pituitary structure on radioimaging. Due to the rarity of its occurrence the prevalence of IAD as a cause of secondary adrenal insufficiency has not been determined. To our knowledge 200 cases are described in the literature. Impairment of GH secretion has been noted in 20–30% of patients with IAD which is normalized after glucocorticoid replacement.
Case report
This is the case of a 56 y/o female patient initially referred to the endocrine clinic complaining of tiredness, fatigue, weakness, and an elevated TSH level. She reported a history of a previous episode of syncope 10 years before evaluation and three episodes of near syncope 2 years later associated to tiredness, weakness and sweating. Physical exam was unremarkable and she was initially treated for hypothyroidism with levothyroxine. In the subsequent visits the patient complained of worsening tiredness associated to dizziness, nausea and occasional vomiting. A low serum cortisol level with a low ACTH level suggested the diagnosis of secondary adrenal insufficiency. An ACTH stimulation test showed no rise in serum cortisol from baseline. Complete evaluation of anterior pituitary hormones was unremarkable. A pituitary MRI was normal. An insulin tolerance test demonstrated ACTH and GH deficiency. Treatment was initiated with low dose hydrocortisone and symptoms resolved. After 8 months of treatment a glucagon stimulation test revealed persistent ACTH deficiency but GH secretion normalized.
Conclusion
IAD is a rare cause of secondary adrenal insufficiency that can present with nonspecific symptoms and could be potentially fatal in an acute stress period. Prompt recognition is essential to decrease morbidity and mortality. Symptoms of adrenal insufficiency and GH deficiency may overlap therefore it is important to recognize that transient GH deficiency may present with IAD to avoid unnecessary exposure to GH replacement therapy and its potential adverse effects and high cost.

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P867

Sterile pituitary abscess associated with hypophysitis and panhypopituitarism: case report

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Introduction
Pituitary abscess is rare. The incidence is difficult to estimate but two papers indicated numbers $<$1 and 0.6% of all cases of pituitary disease. We present a patient with panhypopituitarism without diabetes insipidus sharing a cystic mass in the pituitary gland.
Case history
A man aged 47 was referred with symptoms of intense, frontal headache since a few months, fatigue and erectile dysfunction with decreased sexual desire. There was no visual impairment. Hormonal workup revealed panhypopituitarism without diabetes insipidus. MRI of the brain showed an inhomogeneous, enlarged pituitary gland with a central cystic lesion. Hormone replacement was started, without subjective clinical benefit and severe headaches remained.
Because of the combination of acute and complete failure of the pituitary gland with intense, continuous headache, the hypothetical diagnosis of hypophysitis was made. On the MR images, features of hypophysitis (meningeal thickening and thickened, enhancing pituitary stalk) were confirmed.
Treatment with high dose corticosteroids (64 mg methylprednisolone) was started. With this treatment the headaches disappeared immediately, however, when the corticosteroids were reduced and stopped, the severe headaches re-occured and treatment had to be restarted.
Surgical resection of the cystic lesion and a diagnostic pituitary biopsy were proposed. A sterile pituitary abscess was found and hypophysitis was confirmed. After surgery, headaches remained, and a control MRI showed an unchanged or recurred cystic pituitary lesion. High dosis corticosteroid therapy (64 mg methylprednisolone) was reinstalled with disappearance of complaints and normalization of pituitary imaging, after which corticosteroid were tapered and stopped. Partial recuperation of hormonal function was established.
Conclusion
Diagnosing pituitary abscess before surgery is very difficult, if not impossible. This patient combined panhypopituitarism based on hypophysitis in the presence of a sterile pituitary abscess.

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P868

Pathological findings in kidneys of acromegalic patients

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Introduction
Acromegaly is an endocrinopathy that affects many different organ systems and leads to multiple comorbidities. Data on morphologic pathology of kidneys in acromegaly is scarce.
Methods
We investigated 19 acromegalic patients (11 male, mean age 57.8 ± 12.1 years) presenting in our outpatient clinic. We evaluated each patient's kidneys by ultrasound, measuring organ dimensions and volume as well as noting any pathologic findings.
Results
With latest recommendations on criteria for cure acromegaly was considered biochemically controlled in seven patients. Equally, seven patients were partially controlled (IGF-I within 30% of the upper limit of normal). Mean duration of disease was 16.1 ± 10.1 years. Renomegaly was found in three patients (16%). A total of 22 simple cysts were found in seven patients (37%), two patients (11%) presented with complex renal masses. Microscopic nephrocalcinosis was detected in five patients (26%), and one kidney stone (13 mm in size) in another patient. Furthermore, we found bilateral obstructive uropathy and one duplex kidney in one patient each. Overall, 17 patients (89%) presented with pathological or anomalous findings.
Conclusion
We found a high prevalence of pathological ultrasonographic findings in a sample of 19 acromegalic patients. Simple and complex renal cysts and nephrocalcinosis were more frequent than described in the literature for non-acromegalic patients. Further research is needed to better quantify our findings and to allow for sub-group analysis.

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P869

A case with acromegaloidism

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Introduction
Acromegaloidism is characterized by features of acromegaly without excessive GH secretion.
Case report
A 24-year-old male presented with acral enlargement and bilateral non-inflammatory wrist and ankle pain. He had coarse facial features, prominent clubbing, enlarged hands and feet. BMI was 21.3 kg/m^2. He did not have a relevant personal and family history. He was not on any medication. Due to his acromegaloid appearance he was referred to endocrinology out-patient clinic with the diagnosis of acromegaly. Basal GH level was 0.6 ng/ml and IGF1 level was 161 ng/ml (N: 115–358 ng/ml). Other anterior pituitary hormone levels and routine biochemical evaluation did not reveal an abnormality other than a slightly increased CRP level (41 mg/l). Fasting glucose level was 99 mg/dl, HOMA-IR was 1.1. RF and anti-CCP was negative. ALP level was within normal limits (93 U/l). Plain films revealed bony changes and the nuclear medicine whole-body bone scan showed bilateral increased tracer uptake in forearms and lower legs. Remaining bones had normal skeletal tracer distribution. The X-ray and scintigraphy results were consistent with hypertrophic osteoarthropathy. Further evaluation did not reveal a secondary cause so he was diagnosed with primary hypertrophic osteoarthropathy. For follow-up he was referred to the rheumatology out-patient clinic where he lived. Treatment with nonsteroidal antiinflammatories provided significant relief of pain.
Conclusion
Presence of acromegaly features without associated biochemical findings may be misinterpreted as mild-early acromegaly or so-called 'burned-out' acromegaly. Clinicians should also keep in mind the phenomenon 'acromegaloidism', although it is a rare condition. An extensive evaluation should be conducted to determine the underlying condition.

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P870

Colon cancer metastatic to the pituitary gland: a case report

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Background
Metastases to the pituitary gland are rare events and usually indicate widespread malignant disease. Most common symptoms of pituitary metastases are diabetes insipidus and visual disturbances. The lung and breast are the most common sites of primary tumors that metastasize to the pituitary gland. Pituitary metastasis of gastrointestinal tractus is extremely rare.
Case presentation
A 53-year-old woman was given chemotherapy for colon cancer with liver metastases. During chemotherapy she complained from polyuria and polidypsia and she was referred to our endocrinology clinic. Water deprivation test was compatible with central diabetes insipidus. The hormones of anterior hypophysis were with in normal limits. Pituitary MRI showed a sellar mass lesion of $7.5 \times 5.5 \times 8.5$ mm in dimesion which was accepted as a metastatic lesion.
Conclusion
The most common malignancies which cause pituitary metastasis are breast and lung cancer. This is an extremely rare case of central diabetes insipidus which is due to pituitary metastasis of colon cancer.

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P871

Acut monocytic leukemia with pituitary involvement; a case report

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İntroduction
CNS involvement is rare in acute monocytic leukemia cases. Pituitary involvement seems much more rarely with unknown frequency. Here, we present a case of AML- M5 (FAB classification) patient with pituitary involvement.
Case presentation
A 29 years old, male patient, admitted to hematology clinic with visual disturbance and poor performance status. Allogeneic hematopoietic stem cell transplantation was performed in 2010 after chemotherapy with diagnosis of acute monocytic leukemia. During follow-up in remission, the patient had visual disturbance in lefte eye and poor performance status. Central facial paralysis and visual loss was found in physical examination and relaps of leukemia was diagnosed. Leukemic infiltration of pituitary gland, infindibulum, optic chiasm and brain parencyhme was seen at cranial MRI. Radiotherapy and dexamethasone therapy were planned. Endocrinologic assesment was made; fasting blood glucose, sodium, potatium, liver and renal function tests were in normal limits. Pituitary hormon levels were all depressed. L-thyroxine replacement was started due to panhypopituitarism. After the initiation of this treatment urine output was noticed 6000–7000 cc per day and serum osmolality decreased from 298 to 96 mOsm/l. Water deprivation test was performed and 5% of body weight was lost; urinary specific gravity was increased by 50% following vasopressin administration. Nasal DDAVP was started with diagnosis of central diabetes insipidus. Polyuria and polydipsia was improved under minirin treatment. Following the completion of radiotherapy treatment the patient was discharged with recommendation of outpatient control.
Discussion
Acute myeloid leukemia (AML) is rarely associated with diabetes insipidus (DI) and hypopituitarism. Adrenal insufficiency and hypothyroidism may mask diabetes insipidus so steroid and thyroxine treatment can cause diabetes insipidus become apparent.

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P872

Late onset *postpartum* diabetes insipidus: a case report

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Introduction
It's well known that any form of diabetes insipidus (DI) can be exacerbated or first become appearent during pregnancy, since increased catabolism of ADH by plasental vasopressinas enzyme. *Postpartum* DI cases mostly presenting as a part of Sheean syndrome and began after *postpartum* first days. There was no any published case of isolated DI that began in the 6th month after deliveration in current literature.
Case
A 37-year-old female patient, admitted to our clinic with complaints of polydipsia and poliüria. She became pregnant by IVF method a year ago. In 6th month after birth polydipsia and polyuria complaints were began.
She had complaints of 10 l water drinking per a day and 3–4 times night urinate. She delivered by cesarean section and had no excess *postpartum* uterine hemorrhage. She had regular menstrual cycle after birth and nursed her baby. She had history of an abortus 5 years ago and no history of cranial travma. Physical examination was unremarkable except of tongue dryness. Fasting plasma glucose, liver function tests and renal function tests were normal. Plasma sodium was 155 mmol/l (136–145) and urine density was 1001. The water restriction test and response to vasopressin test results indicated central DI. Arginin-vasopressin (AVP) nasal spray 1×1 was started. Polyuria, polydipsia and nocturia symptoms were resolved. Sella MRI showed the anterior pituitary gland normal whereas brightness of the posterior pituitary was not seen. The anterior pituitary function tests were within normal limits. She was diagnosed as *postpartum* central DI and discharged with AVP nasal spray one time a day.
Discussion
Most cases of postpartum DI seen with Sheean syndrome and they have become symptomatic within few days after delivery. In our case, development of DI was remarkable in the *postpartum* 6th month. Since, it is not clear that this clinical situation is just coincidental finding or first appearent by triggering postpartum period with unknown mechanism.

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P873

Abnormalities of midline and GH deficiency: about 160 cases

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Introduction
Abnormalities of midline (AML) can be isolated or to be associated to secretory pituitary abnormalities that reflect a developmental defect of the hypothalamic pituitary (HP) region.
Aim
Find AML in GH deficiency (GHD) and see their relationship with the appearance of the HP region and the severity of hypopituitarism (I P).
Population and methodology
160 children (141 ♂, ♀ 19) (IGH) underwent a clinical examination, a hypophysiogramme (test glucagon/propranolol/GH test insulin/GH/cortisol, IGF1, FT_4, TSH, ACTH, Prolactin, urinary density ± test fluid restriction (gonadotropin axis has not been evaluated because prepubertal bone age) and magnetic resonance imaging HH (MRI). The exploration was complemented by a complementary assessment in the presence of visceral malformations.
Results
A ML are found in 60% of cases. Facial malformations are predominant (85%). They are represented mainly by ocular signs (congenital strabismus: 72%) cerebral MRI revealed intracranial abnormalities of midline in 25% of children. Other abnormalities not within the ALM are also associated with IGH in 16% of cases. The AM L are more frequent when there are abnormalities HH region ($P = 0.04$).
The number of combined pituitary deficits is more important when the AM L are present ($P < 10^{-3}$).
The AML presence is independent of the number of abnormal HH region ($P = 0.76$).
Discussion and conclusion
ALM are clinical markers of hypopituitarism. They have to consider a systematic neuroendocrine and visceral exploration. Their presence has a high diagnostic and etiological value because it directs toward to the congenital hypothalamic disorders and permanent déficit. Regular monitoring are necessary.

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P874

Acromegaly and schizophrenia: an incidental association?

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Context
Acromegaly associated to schizophrenia was firstly reported ~60 years ago and, so far it is unclear whether this association is causal or not.
Objective
We report on three new cases and discuss the potential pathophysiological mechanisms of this association.
Results
We report two males and one female diagnosed with schizophrenia and treated for several years with antipsychotics who developed acromegaly due to a GH-secreting pituitary macroadenoma. In all cases the diagnosis of schizophrenia preceded acromegaly with mean disease duration of ~12 years. Antipsychotic therapy was different in every patient. Two patients underwent transsphenoidal surgery. Histopathological study showed mixed GH- and prolactin (PRL)-secreting adenoma in one patient and pure GH-secreting adenoma in the other one. Several pathophysiological mechanisms related to alterations in dopaminergic neurotransmission due to psychiatric disease itself or its pharmacological treatment are proposed and discussed as likely linkage between schizophrenia and acromegaly.
Conclusion
These case reports suggest that schizophrenia and/or its antipsychotic therapy in the long-term might be in relation with the development of GH-secreting pituitary adenomas.

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P875

Pre-surgical medical treatment, a major prognostic factor of remission in acromegaly

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Context
Following the recent evolution in therapeutic strategies for GH-secreting pituitary adenomas, determining optimal individualized patient management is now crucial.
Objective
To determine whether pre-surgical medical treatment (PSMT) in patients with acromegaly improves surgical outcome and to specify thresholds for such a strategy.
Methods and design
This retrospective study included 110 newly diagnosed acromegalic patients operated on between 1997 and 2007 at Timone Hospital, Marseille, France. The mean long-term follow-up period was 52 ± 36.6 months (median 41 months). 64 patients (58.4%) received PSMT (long acting Somatostatin Analogs) during

2–18 months (mean 6.4 months) and all patients underwent pituitary surgery. Remission was based on updated criteria, associating GH nadir after oral glucose tolerance test <0.4 μg/l and normal IGF1 for age, sex and gender at early (3 months) evaluation or at the end of follow-up ($n=95$).
Results
In multivariate analysis, PSMT was significantly linked to early remission (45.3% patients in remission with PSMT vs 26.1% without; $P=0.01$) and to long-term remission (61.1% with PSMT vs 36.6% without; $P<0.01$). Duration of PSMT was not significantly different in cured or non-cured patients, at both evaluations. At 3 months and at long-term evaluation, pre-treated and non pre-treated groups were comparable for the main confounding factors except for IGF1 at diagnosis which was higher in patients with PSMT. PSMT was more beneficial for patients with somatotroph adenoma larger than 15 mm. Noteworthy, no patient with a more than 18 mm adenoma or a mean GH exceeding 35 ng/ml at diagnosis was cured by surgery without PSMT.
Conclusions
Pre-surgical medical treatment significantly improved short and long-term remission in acromegalic patients, independently of its duration and main confounding factors, and seemed to be especially interesting in adenomas larger than 15 mm.

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P876

Preoperative octreotide treatment of acromegaly: long-term results of a randomized, controlled study

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Objective
Early postoperative results for the Preoperative Octreotide Treatment of Acromegaly (POTA) study has been published, and like later randomized studies we demonstrated a beneficial effect of presurgical treatment with somatostatin analogues (SSA) in GH-secreting macroadenomas when evaluated 3–4 months postoperatively. However, concerns about a potential lingering effect of SSA and thereby potential false positive results have been raised. The objective of this study was to evaluate the long-term surgical cure rates.
Methods
Newly diagnosed patients were randomized to either 6 months pretreatment with octreotide LAR ($n=32$) or to direct surgery ($n=30$). Of them, 51 (26/25) had macroadenomas. The patients were evaluated 1 and 5 years postoperatively. Cure was defined as a normal IGF 1 level combined with nadir GH <2 mU/l in an oral glucose tolerance test, without having received postoperative treatment.
Results
The proportion of patients receiving postoperative acromegaly treatment was equal in the two groups both 1 and 5 years postoperatively. When using the combined criteria for cure, 10/31 (32%) of all adenomas and 10/26 (38%) macroadenomas were cured in the pretreatment group compared to 8/30 (27%) in total and 6/25 (24%) macroadenomas in the direct surgery group 1 year postoperatively ($P=0.63$ in total group and $P=0.27$ for macroadenomas). Five years following operation, the cure rate in the pretreatment group was 11/27 (41%) in total and 9/22 (41%) in macroadenomas versus 8/26 (31%) and 6/22 (27%) in the direct surgery group ($P=0.45$ and $P=0.34$).
Discussion
These long-term data from the POTA study does not prove a beneficial effect of SSA presurgical treatment. Still, in absolute numbers, an ~50% increase in cure rate is found. We can not exclude that this is due to lack of power resulting in a type 2 statistical error.

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P877

Evidence for truncated somatostatin receptor 5 modulation of therapy response to somatostatin analogues in two patients with acromegaly and severe headache

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Objective
Pituitary GH-secreting adenomas have unique 'fingerprints' of somatostatin receptor (sst) expression, which are targets in treatment of acromegaly with somatostatin analogues (SSAs). However, a significant expression of sst is not always related to the biochemical response to SSAs. Headache is a common complaint in acromegaly and considered a clinical marker of disease activity, but pathophysiology of acromegaly-associated headache is not yet elucidated. Hormone secretion, tumour size, and traction of pain-sensitive intracranial structures have been implied. SSAs are reported to have an own analgesic effect, but the sst involved are unknown. We investigated two acromegalic patients with severe headache and no biochemical effects of octreotide, but a good response to pasireotide. Response to SSA therapy was discussed in relation to immunohistochemical expression of sst1–5 in tumour cells, including a truncated sst5 variant (sst5TMD4).
Case reports
Case 1 had no biochemical or analgesic effects of octreotide, a semi-selective SSA, but a rapid and significant effect of pasireotide, a pan-SSA. Case 2 demonstrated discordance between analgesic and biochemical effects of octreotide, in that headache disappeared, but without biochemical improvement. In contrast, pasireotide normalized IGF1. Immunohistochemical analyses showed that both adenomas had strong membranous expressions of sst2a in 50–75% and sst5 in 75–100% of tumour cells, respectively, and sst5TMD4 was expressed in 20–57% of tumour cells.
Conclusions
A poor biochemical response to octreotide was associated with tumour expression of a truncated sst5 variant, despite abundant sst2a expression, suggesting an influence from variant sst5 on common sst signaling pathways. Furthermore, unrelated analgesic and biochemical effects of SSAs indicated a complex pathogenesis of acromegaly-associated headache. Finally, assessment of truncated sst5 in addition to full length sst could be important for a choice of postoperative SSA treatment of pituitary GH-secreting adenomas.

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P878

A case with macroprolactinemia and gigantomastia responding to cabergoline treatment

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Macroprolactinemia is reportedly 10–25% in patients with hyperprolactinemia (1). Prolactin plays a major role in breast development (2). Macromastia, gigantomastia, breast hypertrophy are used interchangeably (3). Most authors conclude that gigantomastia cannot be treated medically and only resolves with surgical manoeuvres (4). We report a case with gigantomastia diagnosed with macroprolactinemia and treated with cabergolin.
Case
A 44-year-old woman admitted to our clinic with 6 months history of breast enlargement, nipple discharge, mastalgia, and back pain. She requested surgical reduction. Her menstrual cycles were regular. There was no history of chronic disease or drug use. The breasts are firm to palpation and diffusely tender. The superficial veins are prominent and dilated. She had no fever, erythema,

ulceration of the breast skin. Breast circumference was 116 cm. Galactorrhea was present. Hormonal assay revealed hyperprolactinemia (prl:87 ng/ml) and macroprolactinemia. Other anterior pituitary hormons were normal. Hook effect was not detected. MRI showed 6 mm pituitary adenoma. Breast ultrasound and mammography were normal. Cabergoline 0.5 mg/week was started. Macroprolactinemia and hyperprolactinemia were normalized within 1 month. 1 and 2 months later, breast circumferences were 110 and 108 cm respectively, although galactorrhea continued. Patient was satisfied with postmedical recovery and gave up operation demand.
Conclusion
Smaller proportion of patients with macroprolactinemia has signs and symptoms of hyperprolactinemia; galactorrhea is present in 20%, oligo/amenorrhea in 45%, and pituitary adenomas in 20% (5). Two explanations are possible in our case: coexistence of pituitary adenoma and macroprolactinemia or macroprolactin production by pituitary tumor itself. Literature data have provided evidence in favor of both possibilities (6). Cabergolin treatment seems to be safe and effective in controlling gigantomastia and macroprolactinemia without surgical intervention. Although macroprolactinemia is considered to be a benign condition, pituitary imaging, dopamine agonist treatment, and prolonged follow-up should be recommended in some cases (6).

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Comprehensive geriatric assessment of elderly cases with acromegaly

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Introduction
We aimed to determine changes in geriatric assessment of cases with acromegaly.
Methods
26 elderly cases with acromegaly (controlled/uncontrolled: 15/11, F/M: 17/9) were included. 20 age, gender and BMI matched cases without acromegaly composed control group (CG) (F/M: 10/10). Presence of concomitant diseases and educational level were not different between the groups. Cognitive functions were evaluated with Mini Mental State Exam (MMSE), affective status with Geriatric Depression Scale, activities of daily living with Katz index, instrumental activities of daily living (IADL) with Lawton scale, and nutrional status with Mini Nutritonal Assessment. For body composition bioimpedance analysis, for functional mobility 6-m walking speed test (6 m-WST) and for overall muscle strength handgrip-strength test were performed. BMI, GH and IGF1 levels, an extensive laboratory evaluation were also obtained.
Results
The mean age of acromegaly cases and CG was 67.3 ± 6.3 and 67.2 ± 4.7 years respectively ($P=0.9$). Score of MMSE was lower in acromegaly (24.5 (IQR: 21.4–26)) in comparison to CG (29 (IQR: 28–30)) ($P=0.001$). In the entire cohort cognitive functions decreased as IGF1 levels increased ($r=-0.4$, $P=0.02$). In acromegaly group as well as in the whole cohort IGF1 was related with decreased IADL ($r=-0.4$, $P=0.03$ and $r=-0.4$, $P=0.02$ respectively). More cases with acromegaly had risk for malnutrition (acromegaly/CG: 9/1, $P=0.02$). In acromegaly GH and IGF1 were positively correlated with the results of 6 m-WST ($r=0.4$, $P=0.04$ and $r=0.5$, $P=0.02$), showing decreased functional mobility with increased GH and IGF1 levels. Similarly, in the entire group GH and IGF1 levels were positively correlated with 6 m-WST ($r=0.3$, $P=0.004$ and $r=0.4$, $P=0.01$). In acromegaly increased GH was associated with decreased right-sided handgrip-strength ($r=-0.4$, $P=0.03$).
Conclusion
Acromegaly causes an additional burden on cognitive functions, risk of malnutrition, functional mobility and instrumental daily living activities in geriatric population. A multidisciplinary, more comprehensive approach is necessary for acromegaly cases especially when they get elderly.

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Somatostatin analogue treatment of a TSH secreting adenoma presenting with accelerated bone metabolism and a pericardial effusion

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Objective
To report the unusual presentation of a thyrotropinoma in a patient with: i) accelerated bone turnover, evident as osteopenia and increased serum alkaline phosphatase level, and ii) a pericardial effusion, years before diagnosis, that resolved completely following surgery and somatostatin analogue treatment.
Case report
A 38-year-old man had been treated for years for presumed hypothyroidism with thyroxine supplementation based on elevated TSH levels before the clinical suspicion of a TSH secreting pituitary adenoma (TSHoma) was raised. During that time period there was a persistent elevation of alkaline phosphatase and associated osteopenia that had been attributed to vitamin D deficiency, although vitamin D supplementation was of no benefit. He concurrently developed a pericardial effusion of no apparent cause despite a comprehensive diagnostic work up and was treated surgically. Recurrence of a pericardial effusion and a pleural effusion developed a few months after initial treatment. At that time thyroxine was discontinued, a pituitary macroadenoma was diagnosed and TSHoma was confirmed by classical biochemical features and an elevated a-glycoprotein subunit. After surgery, due to incomplete resection and persistent although mild elevation of a-glycoprotein subunit, an octreoscan was performed and, based on a positive scan, treatment with octreotide long acting repeatable (LAR) was initiated, to which he had an antitumor and antisecretory response. Shortly after initiation of medical treatment a recession of the pericardial effusion was noted and alkaline phosphatase levels were normalized.
Conclusion
Increased bone metabolism due to a hyperthyroid state induced by a TSHoma may be anticipated. However, effusions (pericardial, pleural) have only rarely been reported in combination with hyperthyroidism. To our knowledge this is the first case of a TSHoma accompanied by pericardial and pleural effusions that both dissolved after treatment of the adenoma.

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P881

Normal health-related quality of life can be achieved in patients with functional pituitary adenomas having surgery as primary treatment

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Introduction
Previously, impaired health-related quality of life (HRQoL) was reported in patients with functional pituitary adenomas (FPA) and/or hypopituitarism. Our aim was to assess HRQoL in a cohort of FPA patients who underwent transsphenoidal surgery as primary treatment at our University Central Hospital between years 2000 and 2010.
Design
A cross-sectional study including an age- and gender-standardized sample of the general population.
Patients and methods
HRQoL was assessed by the 15D questionnaire in 100 FPA patients (acromegaly $n=47$, Cushing's disease $n=21$, prolactinoma $n=26$, TSH-adenoma $n=2$, gonadotropinoma $n=4$), operated on a mean of 7.4 years (range 2.1–13.0) earlier. To achieve hormonal control, medical therapy, re-operation ($n=6$) and/or radiotherapy ($n=7$) were given when appropriate. Replacement therapy was initiated for hypopituitarism ($n=43$ (43.9%)). The results were compared to those of an age- and gender-standardized sample of the general population ($n=6120$). Determinants of HRQoL were assessed by Mann–Whitney U test, one-way ANOVA or multiple regression analysis.

Results
Mean total 15D scores were slightly better in patients compared to controls (0.917 vs 0.905, $P<0.05$). In single dimensions, FPA patients scored better with regards to mental function, and discomfort and symptoms ($P<0.05$ and $P<0.001$, respectively). In FPA patients, age at time of survey, number of co-morbidities, hormone and thyroxine replacement therapy predicted impaired HRQoL, but not hydrocortisone replacement, radiotherapy treatment or time after surgery. Only age and comorbidities ($P<0.001$) and thyroxine replacement therapy ($P<0.001$) were independent predictors of impaired HRQoL.
Conclusions
Today, it is possible to achieve normal HRQoL in FPA patients. In our University Hospital cohort, this was achieved by transsphenoidal surgery for all and medical therapies and radiotherapy as appropriate. FPA patients demonstrate an age-related decline in HRQoL, similar to that seen in the population in general. Hypopituitarism, especially TSH deficiency associated with impaired HRQoL.

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P882

Comparison of the effectiveness of bromocriptine and cabergoline treatment of microprolactinomas in women based on results of dynamic pituitary gland MRI

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Objective
The aim was to compare the effectiveness of the bromocriptine and cabergoline treatment of the women with microprolactinomas.
Materials and methods
82 women with microprolactinomas were included in this study (51 patients received bromocriptine (Group 1) and 31 – cabergoline (Group 2)) with MRI-control after the first year of treatment (11 women from Group 1; 7 – from Group 2), the second (27 women from Group 1; 15 – from Group 2) and third year of treatment (13 women from Group 1; 9 – from Group 2). The drug dosage was titrated until the normalization of the serum prolactin level. The selective method of the statistical analysis was used. The changes were considered as positive if the size reduction of microprolactinomas was not $<15\%$, negative – the enlargement was not $<15\%$. Insignificant or absent changes were considered as no dynamics.
Results

MRI-dynamics	Group 1 1 year ($n=11$)	Group 2 1 year ($n=7$)	Group 1 2 year ($n=27$)	Group 2 2 year ($n=15$)	Group 1 3 year ($n=13$)	Group 2 3 year ($n=9$)	Group 1 ($n=51$) (%)	Group 2 ($n=31$) (%)
Positive	2	4	9	8	1	4	12 (24%)*	16 (52%)*
Negative	2	0	1	0	3	1	6 (11%)	1 (3%)
Without dynamics	7	3	17	7	9	4	33 (65%)	14 (45%)

*Group 1 vs Group 2 $P<0.05$.

Conclusions
It was pointed out that the achievement of positive dynamics in women with microprolactinomas receiving treatment with dopamine agonists for 1–3 years was more than two times more frequently with cabergoline than bromocriptine. The findings suggest that cabergoline is preferable to bromocriptine in the treatment of the women with microprolactinomas.

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P883

A case of become pregnant woman with active acromegaly during Octreatide LAR treatment

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Pregnancy in active acromegaly at reproductive age is very rare occurrence due to hyperprolactinemia, hypogonadism and side effects of treatment of acromegaly. Only a few reports were described in medical literature by now.

We report a 31-year-old woman ongoing active acromegaly despite who received Octeatide LAR 30 mg treatment monthly for the control of GH and IGF1 excess until realized her pregnancy. A GH secreting pituitary macroadenoma (tumor size 2 cm) was diagnosed 3 years ago and twice pituitary transsphenoidal surgery was undergone. Octreatide LAR treatment was started after surgery because of uncontrolled acromegaly. Octreatide LAR treatment was withdrawn as soon as possible after positive pregnancy test. But, she had noticed her pregnancy after 3 weeks from Octeatide LAR injection. During pregnancy, serum IGF1 and GH levels increased gradually. No pregnancy complications were observed and a healthy girl was born at full-term. Lactation was lost spontaneously after *postpartum* 5 months. Pituitary MRI after the delivery was performed. *Postpartum* minimally tumor growth in related to pregnancy was observed in pituitary MRI. But, impaired glucose tolerance was developed after delivery.
It is not clear whether Octreatide LAR therapy should discontinue after confirmation of pregnancy in acromegaly. According to date, no adverse effects related to Octreatide LAR therapy were noted in pregnancy. In case of pregnancy, Octreatide LAR therapy in acromegaly may interrupt until established more safely data. Long-term effect of Octreatide LAR treatment is not known at the fetus even if feasibility and safety of treatment with short-acting octreotide in acromegalic women during pregnancy was indicated.

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P884

Register of sellar tumors: RESET: diagnostics and therapy of acromegaly in Czech and Slovak Republics

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Acromegaly is usually diagnosed after several years of duration. The multimodal therapy – surgery, radiotherpy, pharmacotherapy – is necessary in the majority of patients. Register of sellar tumors (RESET) collecting data of patients from eight tertiary centers in the Czech and Slovak Republics since the year 2000 was established in 2008.
Aim of analysis
Evaluation of diagnostics of acromegaly and effectiveness of its treatment in a daily practice in CR and SR in a period 1.1.2000–3.9.2013.
Patients and results
343 patients (185 + 158 from CR a SR, resp., 189 women, mean age at diagnosis 49 years; for men 46 and for women 52 years). Median time of follow-up was 39.3 months. Three quarters had macroadenoma. In the time of diagnosis 44% of patiens had arterial hypertension (38%) or diabetes mellitus (17%), respectively both (11%). Operated were 81% of patients (reoperated 5%); 93% of operations were transsfenoidal. Normalised IGF1 3 months after surgery was in 54.5% of patients with microadenoma and in 42.4% with macroadenoma. Residual hormonal activity after surgery was treated in the majority of patients with combined radiotherapy and pharmacotherapy. Irradiated were 166 patients and 91% of them underwent radiosurgery with gamma-knife. Long-term pharmacotherapy applied was with somatostatin analogs in 90, dopamine agonists in 69 and with pegvisomant in 37 patients; either alone or in combination. Patients with operation as part of the complex therapy had faster suppression of hormonal activity.
Conclusions
Acromegaly is a serious disease frequently complicated with hypertension and diabetes mellitus. 75% of patients have macroadenoma. The fastest suppression of disease activity is achieved when therapy comprise surgery, alone or in

conjunction with other modalities. An individually tailored multimodal therapy is necessary in the majority of patients.
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P885

Study Design of a Phase II trial of pasireotide s.c. alone or in combination with cabergoline in patients with Cushing's disease

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Background
Dopamine and somatostatin receptors on corticotroph pituitary adenomas are targets for medical treatment of Cushing's disease (CD). Data indicate synergistic effects between pasireotide and cabergoline in improving biochemical control rates and clinical features in patients with CD.
Objective
To evaluate safety and efficacy of pasireotide alone or with cabergoline in patients with CD.
Methods
Patients: adults with confirmed diagnosis of CD (persistent/recurrent/*de novo* not considered candidates for pituitary surgery). Group 1: pasireotide-naïve patients or who had discontinued pasireotide earlier for lack of efficacy; Group 2: patients currently receiving MTD of pasireotide monotherapy for $\geq$8 weeks, but biochemically uncontrolled (mean UFC (mUFC) > ULN; mean of three samples with 2/3 > ULN). Design: phase II, multicenter, prospective, international, open-label, non-comparative. Target enrollment = 128 (Group 1 = 68; Group 2 = 60). Treatment (stepwise): Group 1: pasireotide s.c. 600 µg bid for 8 weeks; if uncontrolled, dose increased to 900 µg bid for 8 weeks; if uncontrolled, pasireotide s.c. 900 µg bid + cabergoline 0.5 mg qd for 8 weeks (if intolerant of pasireotide 900 µg bid, 600 µg bid allowed); if uncontrolled, cabergoline dose increased to 1 mg qd for 8 weeks. Group 2: pasireotide (300/600/900 µg bid) s.c. + cabergoline 0.5 mg qd for 8 weeks; if uncontrolled, cabergoline dose increased to 1 mg qd for 8 weeks. For both groups, dose modifications for cabergoline due to safety are allowed. Endpoints: primary: proportion of responders (mUFC $\leq 1.0 \times$ ULN) in i) Group 1: with pasireotide alone or with cabergoline at wk35 ii) Group 2: with pasireotide + cabergoline at wk17. Secondary: actual and percentage change in mUFC from baseline to study end; proportion of patients attaining mUFC $\leq 1.0 \times$ ULN, proportion of UFC responders or patients having $\geq$50% reduction from baseline in mUFC at each scheduled visit; shift from baseline in clinical signs. No formal hypothesis testing planned. Proportion of patients (95% CI) attaining primary endpoint will be reported.
Conclusions
This study will assess safety and efficacy of pasireotide in combination with cabergoline as a stepwise approach in the treatment of CD.
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P886

An acromegalic patient with history of renal transplantation

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The association of acromegaly and end stage renal disease was not reported before. Here, we present a case of 57 years old male patient who had been followed with the diagnosis of 13 years of acromegaly and 18 years of type 2 diabetes at another center until 2005 when he was admitted to our outpatient clinic. He had been operated for a pituitary macroadenoma 13 years ago and followed without treatment for acromegaly. He was treated with long acting insulin and he was metabolically under control (HbA1c 5.7%) for diabetes. Somatostatin analogue (octreotide LAR) treatment was initiated because of high GH response to oral glucose tolerance test and IGF1 levels accepted according to age and sex. During follow-up his blood pressure elevated, trandolapril and verapamil combination was added to treatment and when he was screened for diabetes complications retinopathy and nephropathy (4.1 g/24 h proteinuria) was discovered. After diagnosis of nephropathy, his renal functions deteriorated very quickly, dialysis and renal transplantation was performed from a cadaver for end-stage renal disease in 2008. Octreotide LAR treatment was suspended for 3 months. He received immunosuppressive treatment (everolimus, mycophenolic acid, and prednisolone) and intensive insulin treatment for elevation of blood glucose levels after the transplantation. Until now he is metabolically under control for diabetes and renal functions as well as acromegaly. According to our search, this is is the first case reported in the literature and it can be concluded that in the work-up of acromegaly and diabetes clinicians should be alert for renal complications.
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P887

Anterior and posterior pituitary functions in male prolactinomas

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Introduction
Male prolactinomas are very rare pituitary tumors as they account for 1/10 among pituitary tumors secreting prolactin. They are usually larger and more aggressive than female ones. The gonadal deficit due to multi factorial mechanism is well known, but other deficiencies are diversely appreciated. Our aim was to analyze anterior and posterior pituitary functions in a large series of male prolactinomas.
Subjects and methods
117 male prolactinomas were analyzed. Their median age was 37.9 $\pm$ 13 years (15–79), median prolactin = 4558 $\pm$ 8039 ng/ml (67–34 858), median tumor height = 40.2 $\pm$ 22.9 mm (3–13). 42.7% were giant ($\geq$4 cm) and 71% were invasive (invasion of one or both cavernous sinuses). Apart from prolactin, all had hormonal assessment based on cortisol and ACTH, testosterone, FSH and LH, GH $\pm$ IGF1, TSH and thyroxin (free T_4), and posterior pituitary exploration based on 24 h urine quantification and urine specific gravity.
Results
0.85% (n = 1) had posterior pituitary deficit, 80.7% had gonadal deficit and 75% had two or more anterior pituitary deficits.
Conclusion
In this large series of male prolactinomas, posterior pituitary deficit is exceptional (<1%), but anterior pituitary deficiencies are very common because of giant and or invasive tumors.
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P888

Hyperprolactinemia and chiasmic syndrome in patients with non functioning pituitary tumors

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We investigated 49 patients with non-functioning pituitary macroadenomas: 11 males, 38 females, age 31–78 y.o. (median 61). Extrasellar tumor expansion was observed in 46 (93.9%) patients: suprasellar – 41 (83.7%), laterosellar 27 (55.1%), and infrasellar 18 (36.7%) patients; combined types of extrasellar expansion – 36 (73.5%) patients.
Prolactin levels (PRL) varied from 115 to 1495 mU/l, hyperprolactinemia was found in 27 (55.1%) patients, macroprolactinemia and symptomatic hyperprolactinemia were excluded. PRL were correlated with vertical (r = 0.65; P < 0.001), frontal (r = 0.53; P < 0.001), and sagital (r = 0.5; P < 0.001) size of pituitary tumor and with total tumor volume (r = 0.6; P < 0.001).
Chiasmic syndrome (ChS) was observed in 33 (67.3%) of patients with MR-signs of chiasm compression by pituitary tumor. Prolactin levels, tumor size and total tumor volume were significantly higher in patients with ChS compared with without ChS (median (min; max)): prolactin 832 (160; 1495) vs 234 (115; 1056) mU/l; vertical size 25 (15; 50) vs 12 (8; 17) mm; frontal size 23 (12; 62) vs 14 (5; 33) mm; tumor volume 7680 (1190; 63 800) vs 1441 (280; 4350) mm^3 respectively (P < 0.001 for all). All patients with tumor volume > 4360 mm^3 and/or vertical tumor size > 18 mm, frontal size > 19 mm had chiasmic

syndrome. A strong correlation was found between severity of chiasmic syndrome and tumor volume ($r=0.8$, $P<0.001$), prolactin levels ($r=0.5$; $P<0.001$). Among 33 patients with ChS, 30 (91%) persons had elevated prolactin levels.

Thus, in cases of nonfunctioning pituitary tumors prolactin levels were <1500 mU/l in our study. As prolactin levels correlated not only with vertical but also with frontal and sagital sizes of tumor, we suggest that not only pituitary stalk prelum but also intrapituitary compression of normal hypophysis might play role for dopamine control dysregulation. Vertical tumor size >18 mm, frontal size >19 mm, and hyperprolactinemia are strongly associated with chiasmic syndrome.

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P889

Acromegalic arthropathy: clinical presentation, treatment and quality of life

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Introduction

Arthropathy affects the majority of acromegalic patients and is a major cause of morbidity, absenteeism and impaired quality of life. GH excess and increased levels of circulating IGFI result initially in a marked thickening of the soft tissues and cartilage. Along with disease progression, there's subperiostal bone neoapposition, cartilage regressive phenomena and bone structural changes. We aimed to investigate prevalence, clinical presentation, treatment and impact on quality of life of arthropathy in acromegalic patients.

Description of methods

Demographic and clinical data collection and cross-sectional descriptive study (convenience sample, by telephone) regarding onset, duration and severity of articular symptoms (according to the visual analog scale) and AcroQol-physical dimension.

Results

Off 168 patients, 17 (10.1%) died, 64 (38.1%) had outdated contacts, 39 (23.2%) didn't want to participate/didn't answer the call but 48 (28.6%) did. Off these, 33 (68.8%) were women, mean weight 82.1 ± 14.6 kg (BMI 30.4 ± 4.0 kg/m^2), average disease duration of 11.3 ± 9.0 years; 46 (89.6%) were submitted to surgery: 22 (48.9%) are cured, two waiting for results and 19 on medical treatment. Eight (16.7%) performed orthopedic surgery in a mean time of 11.1 ± 8.53 years: one hip replacement, one arthrodesis of foot, one cervical laminectomy, one knee cartilage excision, five knee arthroplasties, one shoulder arthroplasty. Regarding clinical presentation: 17 (35.4%) were asymptomatic, 10 (20.8%) presented knee pain, ten arthralgias, 5 (10.4%) shoulder + knee pain, other being more rare. Average pain intensity was 5 ± 2.5 with joint complaining starting 6.0 ± 6.8 years after diagnosis. In what concerns to AcroQol-phsyical domain, 27.1% referred decreased performance at work or usual tasks and 64.6% arthralgias.

Conclusion

The majority of acromegalic patients had moderate/severe joint complaints and impaired work performance and almost a fifth was submitted to orthopedic surgery. Arthropathy and quality of life should be carefully evaluated in acromegalic patients, despite successful long-term treatment.

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P890

Analysis of metabolic alterations within the normal appearing brain in children with GH deficiency: MR spectroscopy and hormonal correlation

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Purpose

The pathogenesis of idiopathic GH deficiency (GHD) in children, including possible cerebral metabolic alterations, remains unclear. The aim of the study was to evaluate the metabolic changes within the normal appearing brain in children with GHD using MR spectroscopy (MRS) and to correlate MRS measurements with hormonal concentrations.

Materials and methods

71 children with GHD (mean age 6.9 years) and 11 healthy controls (mean age 8.4 years) were enrolled in the study. The MRS examinations were performed on 1.5T scanner. Voxels were located in the posterior cingulate gyrus (PCG) and the left parietal white matter (PWM). The NAA:Cr, Cho:Cr and mI:Cr ratios were analyzed in both groups. There were also evaluated correlations between the metabolite ratios and hormonal concentrations: GH in two stimulation tests and GH during the night, as well as IGF1 and IGFBP3 levels.

Results

There was statistically significant ($P<0.05$) decrease of the NAA/Cr ratios in PCG and PWM in children with GHD compared to the normal subjects. Other metabolite ratios showed no significant differences. We found also statistically significant positive correlations between NAA/Cr ratio in PWM and IGFBP3 level, as well as GH concentration in stimulation test with glucagon.

Conclusion

The reduction of NAA/Cr ratios may suggest loss of neuronal activity within normal appearing grey and white matters in children with GHD, thus MRS could be sensitive biomarker of cerebral metabolic disturbances associated with GHD and additional indicator for therapy with recombinant GH.

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P891

Pituitary non-secreting micro-incidentalomas and endocrine dysfunctions: a retrospective analysis in 236 Romanian patients

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Introduction

The pituitary non-secreting microadenomas (or incidentalomas) are frequently diagnosed over the last decades thanks to imagery scan progresses and access. The gonadal dysfunction, as well as other pituitary deficiency is related to common genetic backup (+/− other pituitary dysfunctions) or may be incidental.

Aim

We analyzed the endocrine profile in pituitary incidentalomas (microadenomas).

Material and method

A retrospective study was performed in patients evaluated by computed tomography or magnetic resonance, and by the endocrine profile, and confirmed with pituitary incidentalomas at C.I.Parhon National Institute of Endocrinology, Bucharest, since 1994 up to present. The exclusion criteria were age <14 years.

Results

236 cases of non-functioning adenomas of <1 cm diameter were included. The female:male ratio was 13.7. Average age at diagnosis of the tumor was 40.9 years. The endocrine profile indicated mean IGF1 levels of 223.8 ± 79.1 ng/ml (normal <240 ng/ml). The minimum GH level during the oral glucose tolerance test was 0.2 ± 0.5 ng/ml. The mean serum prolactin was 11.16 ± 8.4 ng/ml (normal <20 ng/ml). One fifth of the patients needed or were under levothyroxin therapy (with primary hypothyroidism). 0.8% of the cohort had persistent hypogonadotropic hypogonadism (no specific genetic tests were performed). 2.4% of the patients associated partial GH deficiency, and 2.4% had partial adrenal secondary insufficiency. No correlation between tumors size and the endocrine disturbances was found. The age of diagnosis in patients with hypogonadotropic hypogonadism was statistically significant lower than the patients without endocrine disturbances and pituitary incidentalomas ($P<0.05$).

Discussions

Gene defects but also autoimmune disturbances might underlie pituitary deficiency. In any of these cases the imagery scan may provide microadenoma aspects.

Conclusion

The pituitary incidentaloma might be associated with pituitary deficiency in $<3\%$ in a population aged over 14 years that was not previously preselected based on the clinical endocrine phenotype.

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P892

Pituitary incidentaloma: an age-related study in 266 Romanian patients

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Introduction
The pituitary tumors which are considered pituitary incidentalomas are accidentally discovered at pituitary scan and they associate a lack of pituitary hyper-secretion. Opposite to what generally are considered for adrenal incidentalomas, the pituitary incidentalomas are more frequent with years of life.
Aim
We analyzed the incidentaloma sizes related to decades of age.
Material and method
This is a retrospective study in patients confirmed with pituitary incidentalomas at baseline and follow-up. They were all admitted for different motives at C.I.Parhon National Institute of Endocrinology, Bucharest, Romania. The inclusion criteria were tumors of maximum 1.1 cm at baseline, and confirmed non-secreting profile.
Results
266 patients were analyzed. The decades analyze was the following. Decade 1 (between 11 and 20 years) included 20 patients (15 women and five men) with mean diameters: 0.55 ± 0.21 cm, and 0.4 ± 0.15 cm. Decade 2 (between 21 and 30 years) included 44 patients (41 women and three men) with mean diameters of 0.6 ± 0.29 cm, and 0.39 ± 0.11 cm. Decade 3 (between 31 and 40 years) included 69 patients (65 women and four men) with mean diametes of 0.56 ± 0.41 cm, and 0.2 ± 0.1 cm. Decade 4 (between 41 and 50 years) included 58 patients (women:men ratio = 57/1) with average diameters of 0.56 ± 0.3 cm, and 0.26 ± 0.12 cm. Decade 5 (between 51 and 60 years) included 53 patients (49 women and four men) with diameters of 0.53 ± 0.36 cm, respective 0.16 ± 0.1 cm. Decade 6 (between 61 and 70 years) included 22 patients (19 women and three men) with diameters of 0.64 ± 0.4 cm, and 0.47 ± 0.38 cm.
Discussion
These observations are related to the baseline tumor features, not with the size dynamic during the years.
Conclusion
Based on these observations, the average diameters of pituitary incidentalomas vary along the decades represented by age at diagnosis in years.

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P893

***Post-partum* pituitary insufficiency: diagnostic challenge**

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Background
Postpartum hypopituitarism, known as Sheehan's syndrome, occurs during a complicated childbirth, due to severe hemorrhage and hpovolemic shock that lead to ischemic necrosis of the pituitary gland.
The aim of the study is to point out the clinical features in *postpartum* pituitary necrosis, so that the disease could be recognize rapidly, to present a laboratory work-up for a postive diagnosis, and also to describe the complications of the untreated cases.
Material and method
The study included 19 patients, admitted to the Clinic of Endocrinology, Timisoara, Romania, in the period 2008–2013. The mean age at diagnosis was 48.8 ± 8.2 years.
Results
After a difficult childbirth with massive hemorrhage, 36.8% of patients were diagnosed during the first weeks with *postpartum* pituitary necrosis, due to agalactia and amenorrhea. The rest of the patients were diagnosed after few years (mean duration until positive diagnosis: 36.2 ± 13.9 months). All women presented at diagnosis an unspecific clinical picture with asthenia, hypotension, palor, secondary amenorrhea, sparse axillary and pubic hair, and hypoglycemia. A percent of 31.5% suffered an emergency histerectomy.
The hormonal determinations confirmed in all patients the central hypogonadism and low levels of prolactin. A percent of 73.6% presented secondary hypothyroidism, 89.4% central adrenal insufficiency, respectively 57.8% GH deficiency. In none of the cases was diagnosed central diabetes insipidus. Four patients presented mild hyponatremia at diagnosis. Pituitary magnetic resonance imaging confirmed empty sella in ten women.
Conclusion
The recognition of the signs and symptoms of *postpartum* pituitary necrosis is mandatory for an early diagnosis and treatment, the mortality and morbidity of the untreated disease being significant.

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P894

'High dose hook effect' in a patient with invasive giant prolactinoma

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Background
Prolactin secreting pituitary adenomas (prolactinomas) is the most common pituitary adenoma. The magnitude of prolactin secretion in prolactinomas is usually proportionate to the tumor's size. Invasive giant prolactinoma is a large prolactinoma (>4 cm in dimension) presenting with serum prolactin levels of >1000 ng/ml and mass related clinical symptoms. Giant prolactinoma is rare and usually presents in men.
Case report
A 52-year-old man was admitted to our hospital with headache, decreased libido, blurred vision and diplopia existing for 6 months. MRI showed a giant pituitary adenoma ($47 \times 35 \times 33$ mm) with extension to sylvian, suprasellar cisterns, invading right cavernous sinus and extension from right of third ventricle to the superior, wrapping the right internal carotid and middle cerebral arteries. The hormon levels at admission showed FSH, 4.48 μIU/ml (NR, 1.5–12.4); LH, 3.75 μIU/ml (NR,1.7–8.6); testosterone 0.736 ng/ml (NR 2.84–8); TSH,0.959 μIU/ml (NR,0.27–4.2); free thyroxin index 1.28 ng/dl (NR, 0.9–1.7) and prolactin, 470 ng/ml (NR, 0–15). Because of apoplexy, patient was promptly operated. Postoperative prolactin level was 470 ng/ml as before. Then prolactin assay was repeated in 1 in 100 dilution of the serum, which was reported as 2060 ng/ml.
Conclusion
The intensity of an antigen-antibody interaction depends primarily on the relative proportion of the antigen and the antibody. A relative excess of either will impair adequate immune complex formation. This is called the 'high dose hook effect'. The high dose hook effect often interferes with the assay result. To overcome the hook effect, the serum sample is diluted and prolactin assayed. In our patient, a 1:100 dilution gets accurate values. We suggest that in order to accurately estimate PRL in patients with large pituitary tumors, PRL should be assayed in 1:100 or even higher dilutions of serum in order to gate an accurate estimate of serum PRL.

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P895

Six cases of FSH/LH positive pituitary adenomas

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Introduction
Immunocytochemistry methods have demonstrated that most of the 'clinically non functional' adenomas are actually gonadotrophin secreting adenomas or gonadotroph adenomas. Gonadotroph adenomas are discovered in patients presenting with visual field disorder. Pituitary imaging almost always demonastrates macroadenoma. Anterior pituitary insufficiency is much more frequent than gonad hyperstimulation. Herein, we present six cases of FSH and/or LH positive pituitary adenomas.
Cases
Six patients (three F, and three M) were diagnosed with pituitary adenoma. Two of our female patients were diagnosed with the complaint of oligomenorrhea because of high prolactin level. The other four patients had visual problems. All of our patients had macroadenoma on pituitary imaging. There were no any

clinical picture of gonadal hyperstimulation. Histochemistry studies have shown that FSH was stained positively in three patients, FSH and LH both were stained in two patients. One patient was found to be only LH positive on histochemical staining. All patients had hypopituitarism. The levels of FSH and LH were not high according to reference range.
Conclusion
Although a significant percentage of non-functioning pituitary adenomas stain positively for LH and FSH, increased levels of circulating FSH and LH are very rare and account for only 10–15% of gonadotrophic adenomas. In our case series, there were no increased level of FSH and LH. FSH and/or LH positivity on histochemistry staining could be related to the issue of invasiveness. The possible mechanisms should be searched to explain the fact that most gonadotroph adenomas do not cause hormone excess but cause hormone deficiency.

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P896

Long-term efficacy and withdrawal of octreotide LAR in acromegaly patients, a prospective single centre study with 4 years follow-up

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Objective
The aim of this single centre prospective open trial was to evaluate the long-term efficacy of octreotide LAR in acromegaly patients and possibility of withdrawal of this therapy.
Methods
In total 17 patients with acromegaly diagnosed at Endocrinology Clinic in Sarajevo, somatostatin sensitive (ten females and six males, age range 37–65 years, six patients with microadenoma and ten patients with macroadenoma) were treated with octreotide. Follow-up period was 4 years (2009–2014). The concentration of human GH (hGH) and IGF-1 were evaluated every 6 months during follow-up period of 4 years, while magnetic resonance imaging was taken every year during follow-up period.
Results
During the first year of treatment ten patients were included. In the second year a further seven patients were involved. During the fourth year of follow-up, the treatment was successful discontinued at four patient, one patient was died due to co-morbidities and at one another patients treatment was off due to kidney cancer; so currently we followed total of 11 patients. During octreotide treatment significantly reduced GH (50.87 ± 10.56 vs 2 ± 0.36 ng/ml, $P < 0.005$), IGF-1 (777.66 ± 118.40 vs 276 ± 80.54 ng/ml, $P < 0.005$) and adenoma size (from 9.6 to 6 mm; $P < 0.01$). GH decrease to <2.5 ng/ml was achieved in 82% of cases; tumor size decrease was achieved in 60% while normalization of IGF-1 was achieved in 91% of the patients, respectively. At 12–24 months of follow-up, 23.5% of acromegaly patients had withdrawn treatment, without recurrence.
Conclusions
Our findings demonstrated that octreotide LAR treatment is very effective in decrease of GH, IGF-1 and tumor size and it's withdrawal, though rare, is possible in well-selected acromegalic patients treated for at least 2 years and considered optimally controlled in hormonal and neuroradiological terms.

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P897

A case of an isolated ACTH deficiency who had a prolonged QT interval

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A 77-year-old female had a loss of appetite, severe fatigue and hyponatremia (127–135 mmol/l) for 2 months. She was diagnosed as depression, and was psychiatrically hospitalized. After admission, she was beginning to take antidepressants, but they did not work at all. To examine hyponatremia, endocrinological examination was done, then low plasma ACTH (2.0 pg/ml) and cortisol (1.3 μg/dl) was found. Brain MRI examination showed no remarkable findings in pituitary. We did a loading test for anterior pituitary function (ACTH/cortisol didn't raise after CRH test to 120 min; ACTH was 2.0 pg/ml and cortisol was 1.0 μg/dl), and diagnosed an isolated ACTH deficiency (IAD). After we started steroid replacement therapy, her fatigue and loss of appetite was disappeared dramatically. Hyponatremia was also improved.
We experienced a case of IAD, which was frequently misdiagnosed as a psychiatric disease. Before steroid replacement therapy, her electrocardiogram (ECG) showed a prolonged QT interval (QTc 0.474 Sec), and after replacement, it was improving (QTc 0.450 Sec).
In Japan, some adrenal insufficiency patients who had a prolonged QT interval experienced fatal arrhythmias, and after steroid replacement therapy, in all cases QT intervals were improved. Under hospitalization, she once had a loss of consciousness before replacement. It is unclear that whether she had an arrhythmia or not because we could not check ECG at that time.
It is said that prolonged QT intervals with adrenal insufficiency are caused by electrolyte abnormalities, reversible myocardial changes due to hypoglycemia and hyponatremia, and, potassium channelopathies on myocardiocytes and so on. It is important to check ECG with adrenal insufficy to avoid fatal arrhythmias.

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P898

Recurrence of hyperprolactinemia after withdrawal of cabergoline in prolactinomas

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Introduction
The optimal treatment duration for prolactinomas to minimize reccurences is not clear. 2011 Endocrine Society Guidelines suggested that cabergoline withdrawal may be safely undertaken after 2 years in patients achieving normoprolactinemia and tumor volume reduction.
Materials and methods
We analyzed 74 patients (mean age $= 46.9 \pm 14.4$, M/F = 19/56, macro/micro = 18/56) bearing a prolactinoma. Patients were divided in 3 groups: Group A (23) treated for 3 years, Group B (23) for a period >3 years but <5 years, and Group C (28) for a period >5 years. Cabergoline therapy was stopped according to Endocrine Society Guidelines. PRL levels were measured 3, 6, 12 and 24 months after withdrawal. Reccurence was defined with PRL levels ≥ 30 ng/ml.
Results
No difference in the three groups regarding the following clinical manifestation was observed: PRL levels 123.2 ± 112.1, 120.9 ± 123.8 and 176.6 ± 154.0, macroadenoma in 13, 17 and 39%, pituitary deficit in 4, 17, and 17% of patients, mean weekly dose of 0.7 ± 0.4, 0.6 ± 0.3 and 0.7 ± 0.4 and PRL levels before withdrawal 17.1 ± 19.6, 11.4 ± 8.8 and 13.8 ± 13.5 in group A, B and C respectively. Recurrence occurred in 34 patients (45.9%): 11 (47%) patients in Group A, 12 (52%) in group B and 11 (39%) in Group C, without differences among groups.
All recurrences occurred within 12 months, in particular: in 15 patients (44%) after 3 months, in 13 (38%) after 6 months and in six patients (18%) after 12 months.
Interestingly, the number of pituitary deficit at diagnosis was significantly higher in patients with recurrence compared with patients in remission at long-term follow-up (eight patients (23%) vs 2 (5%), $P = 0.03$).
Conclusion
Our data are in accordance with the literature regarding recurrence rate and timing after cabergoline withdrawal. In particular, prolonging therapy for more than 2 years does not reduce recurrence rate. Moreover, our study suggest, that patients with pituitary deficit at diagnosis need to be closely monitored.

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P899

Langerhans cell histiocytosis: a case report

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Introduction
Langerhans cell histiocytosis is a rare disease with clonal proliferation of Langerhans histiocytes or their precursors. It is characterized by the infiltration of lipid-laden histiocytic cells or foam cells in skin, viscera, and bone.

Case report
We report a case with gradual onset of polyuria and polydipsia when she was 18 years old. Central diabetes insipidus was diagnosed. Pituitary magnetic resonance imaging (MRI) revealed mild prominent pituitary stalk. Desmopressin was prescribed. Nine years later, progressed photophobia, blurred vision, headache and galactorrhea developed. Pituitary MRI revealed a 0.6 cm infundibular nodule with hypothalamus involvement and perifocal edema. She received Gamma knife therapy. Her symptoms improved and the size of the pituitary lesion decreased.
A palpable mass over right retromandibular region was found when she was 29 years old. Aspiration cytology showed histiocytes. Excision biopsy reported Langerhans cell histiocytosis. Bone scan revealed osteolytic lesions at T10 level of vertebra. Whole body computed tomography reported bronchiectasis at bilateral lung base with multiple tiny nodules and some minor cystic-like lesions. She received adult Langerhan cell histiocytosis LCH-A1 protocol therapy with vinblastine and prednisolone. Radiotherapy over T10 spine was performed. She was kept on hormone supplement for panhypopituitarism. The right neck mass and pulmonary cystic lesions shrank gradually.
Swelling over thyroid gland was noted several months later. Fine needle aspiration cytology from the thyroid revealed infiltration of Langerhans cell. The thyroid size decreased after intensive chemotherapy and radiotherapy.
Conclusion
Langerhans cell histiocytosis is a rare cause of central diabetes insipidus. It can sometimes involve multiple organs, including pituitary, lung, liver, spleen, long bones and dorsolumbar spine. Systemic chemotherapy and hormone supplement should be considered in these patients. Endocrine deficiency often requires lifelong supplement.

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P900

Diabetes insipidus secondary to hypothalamus and pituitary metastasis

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Introduction
The most common cause of diabetes insipidus is idiopathic. However, it may be also seen after metastasis to hypothalamic–pituitary region.
Case
Fifty year old female patient with breast cancer was referred to our clinic with complaints of polyuria and polydipsia. Two years ago, she had diagnosed and after surgery, she has taken three cycles of cyclophosphamide + adriamycin + 5-flurourasil than three cycles dosetaxel and finally seventeen cycles herceptin treatment. PET-CT was normal at March 2013, last chemotherapeutic treatment was given 2 months ago before contact us. In the evaluations, the patient's daily urine volume was found to be ~10–12 l. On physical examination revealed no pathological findings. The patient was hospitalized with a preliminary diagnosis of diabetes insipidus. Water deprivation test revealed central diabetes insipidus. We started desmopressin therapy. After the therapy complaints of polyuria and polydipsia disappeared. Serum osmolarity, serum sodium and urine osmolality levels returned to normal. The nodular lesions that contrasted less than parenchyma in each half of pituitary gland were detected in pituitary MRI and were compatible with metastases. Located in the left hypothalamic–chiasmatic region 3 mm lesion that compatible with metastasis was detected in brain MRI and also multiple metastatic lesions were detected in both cerebral hemispheres. Patient was referred to the medical oncology department.
Conclusion
When investigating the causes of diabetes insipidus, medical history and clinical evaluation is important, and rare causes should be considered. The metastatic tumors of hypothalamic and pituitary region should be noted in a cancer patient.

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P901

How to get surgical remission rates in ACTH-microadenomas close to 100% using minimally invasive approaches for diagnosis and surgery

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Introduction
Pharmacological treatments are still not ideal in ACTH-microadenomas and transnasal-trans-sphenoidal surgery (TSS) is first choice in the treatment of Cushing's disease (CD). The question is how can a nearly 100% remission rate be achieved with minimally invasive diagnostic testing and TSS. In the discussion of the main lecture from an expert from the USA in ECE13, it became clear that in many European centres, like ours, the procedures are less invasive. The developments in our centre treating 100 paediatric Cushing patients will be presented.
Material and methods
Data from published series ($n=55$) of the author will be compared with new data from our recent series ($n=45$). All patients had been operated when MRI and direct transnasal microsurgery (TSS) were established. Special diagnostic methods like inferior petrosal sampling (IPSS) were replaced by ACTH measurement from the cavernous sinus (CSS) in unclear cases without increase of salivary cortisol in the CRH-test or difficult sella anatomy and negative MRI. Micro-histology, micro-doppler and the importance of a micro-suction irrigation system for visualization and minimization of trauma, will be described.
Results
In our first series of 55 cases, IPSS was performed in 13 cases and showed 46% false lateralization. Only with extensive pituitary exploration could most adenomas be removed ($n=52$). Three patients had early successful re-surgery. Second series of 45 cases with refined diagnostic tests and preoperative cavernous sinus sampling ($n=7$), nearly all micro-adenomas were initially detected. Re-surgery became necessary for remission in three. Side effects of surgery were minimal, so children and parents readily accepted re-operation. Thus 98% of 100 patients had long-term remission.
Conclusions
Invasive pre-surgical investigations were mostly avoided, yet with advanced TSS, remission rates of more the 95% could still be achieved. Using feedback from direct postoperative hormone measurements, our remission rates could be improved without increasing complications.

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P902

Prolactin hyperproduction does not predict the risk of glucose metabolic disturbances in patients with acromegaly

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Hypothesis and aim
Acromegaly is frequently associated with impaired glucose tolerance and diabetes, and concomitant hyperprolactinaemia was suggested to add to this effect. We hypothesized that pituitary prolactin (PRL) histopathology and plasma hyperprolactinaemia has a prognostic value in predicting the risk of glucose metabolic disturbances in acromegalic patients. The aim of this study was to examine glucose metabolic outcomes in acromegalic patients with and without histologically verified PRL and GH co-secreting adenomas (GH + ve; and PRL + ve).
Method
79 patients (43 men) who had undergone surgical treatment for acromegaly median 8 years (range: 6 months – 39 years) earlier were included. Clinical and biochemical baseline data were collected from medical records. Patients were divided into two groups based on histopathological evaluation; i) pure GH + ve or ii) GH + ve;PRL + ve co-secreting adenomas. Patients underwent a follow-up visit between January 2012 and January 2013, where blood samples were drawn and an oral glucose tolerance test was performed.
Results
Thirty-five percent of patients had GH + ve; PRL + ve adenomas, whereas 65% had pure GH-production. Patients with GH + ve; PRL + ve adenomas were older ($P=0.04$) than patients with pure GH-adenomas. No significant differences were observed between glucose metabolic outcomes of the two groups, neither at baseline nor at long-term follow-up. Also no differences were found in glucose metabolic outcome between patients with hyperprolactinaemia and patients with normal or low prolactin concentrations.
Conclusion
Pituitary histopathology staining for PRL was not useful in predicting long-term glucose metabolic outcome in acromegalic patients. No association was found between glucose metabolic disturbances, plasma hyperprolactinaemia or histologically verified prolactin production.

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P903

Cushing's disease: the dynamics of serum cortisol concentrations after successful transsphenoidal surgery and the restoration of the adrenal cortex function

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Introduction
Effective surgical treatment of Cushing's disease (CD) is associated with a rapid decrease in the serum cortisol concentration, which requires the introduction of the hydrocortisone replacement treatment. However, the time of restoration of adrenal function is difficult to predict. The aim of the study was to evaluate the dynamics of serum cortisol concentrations after successful transsphenoidal surgery and to determine the time to restore the function of the adrenal cortex.
Methods
The study included 23 consecutive patients (21 females; age: 25.6 ± 8.0) with CD operated on by the same neurosurgeon. The remission was based on standard hormonal criteria. Serum cortisol was determined on the 1st postoperative day and then after 6 weeks, 3, 6, 12 and 18 months. Assays were carried out 48 h after hydrocortisone withdrawal. We considered the lower limit of referral range for cortisol (5.0 μg/dl) as the threshold of adrenal function recovery.
Results
In all cured patients serum cortisol levels on the 1st postoperative day was ≤2.5 μg/dl (median: 1.36 μg/dl). Median serum cortisol after 6 weeks and 3, 6, 12 and 18 months were: 1.0, 2.85, 2.97, 6.0, 10.2 μg/dl respectively. In none of the patients did we observed the return of adrenal function within 6 weeks of surgery. In four patients (17.4%) the adrenal function return was confirmed 3 months after the surgery, in four patients (17.4%) after 6 months, in five patients (21.7%) after 12 months. For the next seven patients (30.4%) return of adrenal function was confirmed after 18 months of follow-up. For the remaining three patients (13%) the serum cortisol concentration was still below 5.0 μg/dl.
Summary
In most cases, the return of adrenal cortex function is expected no earlier than 3 months following the successful surgery for CD. After 18 months of follow-up in more than 90% of the cases one should expect normal function of pituitary–adrenal axis.

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P904

Alternative method of macroprolactin evaluation as a cause of hyperprolactinaemia

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Introduction
Macroforms of prolactin (PRL), the most often macroprolactin (MaPRL), may be the cause of about 25% cases of laboratory diagnosed hyperprolactinaemia. Macroprolactin is usually quantified by polyethylene glycol precipitation, however, the cut-off value (that means the calculated recovery ratio of monomeric PRL) has not been precisely determined and has rather unsatisfactory diagnostic specificity. Therefore, it is suggested that the evaluation of hyperprolactinaemia should include the assessment of prolactin level after macroforms separation – so called real PRL concentration.
Description of methods
Prolactin concentration was measured with the use of Immulite 1000 analyzer. In 245 sera from patients with hyperprolactinaemia, the separation of macroforms was performed by precipitation method. The cut-off value was assumed 40%, so the hormone recovery ≤40% showed MaPRL dominance in serum and recovery >40% indicated monomeric PRL dominance. Then percentage recoveries of monomeric PRL were compared with real PRL concentrations. Prolactin level after macroforms separation exceeding reference range, showed that monomeric hormone dominate in the sample (true hyperprolactinaemia) and hormone concentration within reference range indicated that macroprolactin was the only cause of hyperprolactinaemia (pseudohyperprolactinaemia).
Results
Hyperprolactinaemia due to the large amounts of MaPRL (recovery ≤40%) were detected in 21 subjects. But in this group, despite the dominance of hormone macroforms, real PRL concentration was elevated above manufacturer's reference ranges in nine cases (true hyperprolactinaemia). From among 224 subjects with monomeric PRL dominancy in serum (recovery >40%), in 36 persons the real PRL concentration turned out to be within the manufacturer's reference range (pseudohyperprolactinaemia).
Conclusion
The use of the recovery ratio only to recognize MaPRL dominance as a cause of elevated PRL level, may lead in some subjects to the misclassification of the results and to inappropriate treatment. Therefore, the assessment of real PRL concentration allows to distinguish true and pseudohiperprolactinaemia better.

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P905

Effect of pasireotide on GH, IGF1, IGFBP2, IGFBP3, HbA1C and glucose in patients with inadequately controlled acromegaly: exploratory results from a multicentre, randomized, 24-week study (PAOLA)

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Background
The PAOLA study assessed the efficacy/safety of pasireotide LAR vs continued treatment with octreotide LAR/lanreotide Autogel in patients with inadequately controlled acromegaly. An exploratory objective was to measure changes in various associated biomarkers, including IGF1 and IGFBP2 (released from white fat cells and known to prevent insulin resistance), glucose and HbA1c.
Methods
Adult patients (GH >2.5 μg/l and IGF1 >1.3×ULN) had received octreotide LAR 30 mg/lanreotide Autogel 120 mg monotherapy for ≥6 months and were randomized to: pasireotide LAR 40 mg ($n=65$) or 60 mg ($n=65$); or continued treatment with octreotide LAR/lanreotide Autogel ($n=68$; active control). Blood samples for biomarker assessment were taken before each drug administration.
Results
Pasireotide LAR 40 and 60 mg dose dependently decreased average GH, IGF1 and IGFBP3, without tachyphylaxis of response. Patients who received antidiabetic medication during pasireotide treatment (54% of population) had significantly ($P<0.05$) higher baseline glucose (114 mg/dl (95% CI: 110,119)) and HbA1c (6.2% (6.1,6.4)) levels than patients who received no antidiabetic medication (95.8 mg/dl (92.8,98.9); 5.6% (5.5,5.7), respectively). Peak glucose (115 mg/dl (110,120)) and HbA1c (5.9% (5.8,6.0)) levels in patients who did not receive antidiabetic medication were small compared with those receiving antidiabetic medication (155 mg/dl (143,168); 7.5% (7.1,8.0), respectively). IGFBP2 levels increased from baseline to week 24: 42.4 ng/ml (37.0,48.6) to 62.2 ng/ml (51.9,74.5) and 45.3 ng/ml (39.0,52.5) to 60.1 ng/ml (49.8,72.4) in patients who received and did not receive antidiabetic medication respectively.
Discussion
As elevated GH causes insulin resistance, patients with inadequately controlled acromegaly might be particularly sensitive to developing pasireotide-induced hyperglycaemia. Increased IGFBP2 levels were an unexpected observation given the increased glucose levels.
Conclusions
The effects of pasireotide LAR on glucose homeostasis may be attenuated by increased insulin sensitivity due to the compensatory increase in IGFBP2. Patients not receiving antidiabetic medication (~50% of the population) had significantly lower baseline glucose levels than those who did, and pasireotide-induced hyperglycaemia was mild and decreased over time.

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P906

Somatostatin analogues treatment did not modify glucose control in acromegalic, diabetic subjects

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Context
Acromegaly is chronic insidious disease caused by excessive GH secretion by pituitary adenoma. This leads to overproduction of IGF1 and serious disseminated concequences.
Material
14 acromegalic subjects with diagnosed insulin dependent diabetes on stable octreotide LAR) treatment. Patients did not meet recent criteria of biochemical controlled disease (mean GH 4.6 ng/ml, mean IGF1 2.2-fold upper normal limit).
Methods
Patients were recruited from clinical outpatient database. All glucose self-assessments during three years of observation was captured to include into a database (18 862 assessments). Somatostatin analogue injections were recorded. GH, IGF1, and HbA1c assessments were performed every 3 months.
Results
In whole group over observation period there were increased HbA1c percentage (mean 7.2% SD 1.3 to 7.4% SD 1.6), however insignificant and stable during somatostatin analogue (SA) therapy. Insulin consumption did not increase significantly during observation.
Mean fasting glucose concentrations were stable during therapy. We did not observe fluctuations correlated with intra-injection periods. Mean fasting glucose did not differ pre-injection and 2 weeks after SA injection. Postprandial glucose did not differ significantly throughout post-injection period. We did not see any non-linear correlations between the day after injection and glucose concentrations.
Conclusions
During stable somatostatin analogue treatment in diabetic acromegalic patients, glucose control did not changes during post-injection period. This is additional proof of relatively low fluctuations of SA action during treatment.

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P907

Pasireotide LAR demonstrates superior efficacy versus octreotide LAR and lanreotide ATG in patients with inadequately controlled acromegaly: results from a phase III, multicentre, randomized study (PAOLA)

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Background
Some patients with acromegaly do not achieve biochemical control despite receiving maximum-approved doses of currently available somatostatin analogues. This 24-week, randomized study assessed the multireceptor-targeted somatostatin analogue pasireotide LAR vs octreotide LAR/lanreotide Autogel in patients with inadequately controlled acromegaly.
Methods
Eligible patients: $\geq$18 years with mean GH levels $\geq$2.5 μg/l and IGF1 levels $>1.3\times$ULN (inadequate control) who had received octreotide LAR 30 mg or lanreotide Autogel 120 mg monotherapy for $\geq$6 months. Patients were randomized to: double-blind pasireotide LAR 40 or 60 mg; or continued treatment with open-label octreotide LAR/lanreotide Autogel (active control group). Primary endpoint: proportion of patients with biochemical control (GH $<$2.5 μg/l and normalized IGF1) at 24 weeks. Key secondary endpoint: proportion of patients with normalized IGF1; other secondary endpoints: proportion of patients with GH $<$2.5 μg/l; tumour volume reduction $>$25%; safety/tolerability.
Results
198 patients were randomized: pasireotide LAR 40 mg ($n=65$), 60 mg ($n=65$), active control ($n=68$). Significantly more patients achieved biochemical control (15.4% and 20.0 vs 0%; $P=0.0006$ and $P<0.0001$ respectively) and IGF1 normalization (24.6% and 26.2 vs 0%; $P<0.001$ for both) with pasireotide LAR 40 and 60 mg vs active control at 24 weeks. Furthermore, more patients had GH levels $<$2.5 μg/l (35.4% and 43.1 vs 13.2%) and tumour volume reduction $>$25% (18.5% and 10.8 vs 1.5%) with pasireotide LAR 40 and 60 mg compared with active control. The safety profile of pasireotide LAR 40 and 60 mg was similar to that for the active control group, except for the frequency and degree of hyperglycaemia. The most common adverse events were hyperglycaemia (33.3, 30.6 and 13.6%), diabetes mellitus (20.6, 25.8 and 7.6%) and diarrhoea (15.9, 19.4 and 4.5%).
Conclusions
Pasireotide LAR provides superior efficacy over continued treatment with octreotide LAR/lanreotide Autogel in patients with long-standing, inadequately controlled acromegaly. Pasireotide LAR could become the new standard pituitary-directed treatment in patients with acromegaly inadequately controlled by sst_2-preferential somatostatin analogues.

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P908

High prevalence of autoimmune thyroid diseases in females with prolactinomas: results from a cross-sectional case–control prospective study in a single tertiary referral centre

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Background
Experimental studies have demonstrated that prolactin is a potent immunomodulator influencing both humoral and cell-mediated responses. In accordance with these data, our retrospective studies revealed higher prevalence of autoimmune thyroid diseases in prolactinoma patients compared to general population.
Design
A prospective cross-sectional case–control study was carried out in a single tertiary referral centre.
Aim
Assessment of the frequency of newly diagnosed autoimmune thyroid diseases (AITD) in female patients with prolactinomas compared to sex- and age-matched healthy controls.
Study groups
The study population consisted of 260 females (154 patients and 106 healthy controls).
Methods
Physical exam, thyroid ultrasound and laboratory testing (measurement of antibodies to thyroglobulin, thyroid peroxidase, TSH-receptor, serum TSH and FT_4 levels) were performed in all study participants.
Results
AITD were diagnosed in 29.9% of patients and 10.4% of healthy subjects ($P=0.0002$). Subclinical hypothyroidism was found in 9.7% of patients vs 2.8% of healthy controls ($P=0.044$). Autoimmune hyperthyroidism was observed in 1.3% of all patients.
Conclusions
The prevalence of newly diagnosed AITD and especially the subclinical hypothyroidism due to autoimmune thyroiditis was significantly higher in female prolactinoma patients in comparison to age-matched healthy women. The influence of supraphysiologically increased prolactin levels on the immune response in patients with prolactinomas could be suggested as the most likely explanation for these findings. Based on these results we recommend routine screening for AITD (measurement of TSH, thyroid peroxydase antibodies and thyroid ultrasound examination) in all patients diagnosed with prolactinoma.

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P909

Hormonal deficiency in patients with craniopharyngioma

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Introduction
Craniopharyngiomas are benign epitelial tumors located in the suprasellar region and they are associated to several comorbidities. Our aim is to describe hormonal deficiency and complications after surgery.
Design
Descriptive study of patients that underwent surgery of craniopharyngioma. Data collected included hormonal levels, clinical data and mortality. Quantitative variables with normal distribution are shown as mean and standard deviation and non-normal distribution variables are shown as median and quartiles. Qualitative variables are shown as percentage.
Results
28 patients were researched (53.6% were men), ten of them were diagnosed in childhood with mean age of 47.9 (19.1) years old. Median age at diagnosis was 40 years old (11.5–62.5) and the median of follow-up was 7 years (2.3–15.5). At the time of diagnosis, patients presented visual defects (92.5%), headache (53.8%), polyuria and polydipsia (36.4%), behavior disorders (26.9%), small stature (7.7%), paresthesia (4%) and pubertal development delay (3.8%). The median of the tumor size was 30 mm (28–40). 64% of the tumors extended to the sellar region and 76.9% of the tumors spread out other cerebral regions. After surgery, all patients presented hormonal deficiency: TSH deficiency (100%), ACTH deficiency (96.3%), diabetes insipidus (88.9%), gonadotropin deficiency (88.9%) and GH deficiency (65.4%). After surgery, 18.8% of patients presented an improvement of visual defects. After 5 years of follow-up, the mortality was 17.4%. One patient died few days after surgery. Deceased patients were older at the time of diagnosis of craniopharyngioma (a difference of 28.8 years (CI 95%: 15.6–42.6)) and they presented a bigger tumor size (a difference of 33 mm (13) (NS).
Conclusion
In our study, patients that underwent surgery of craniopharyngioma presented partial hypopituitarism (46.1% of cases) and being absolute hypopituitarism in 53.8% of patients.

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P910

Relationship between early and longer-term tumour volume reduction (TVR) with primary lanreotide Autogel (LAN-ATG) therapy in treatment-naïve acromegalic patients: *post hoc* analyses of the PRIMARYS study

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Introduction
PRIMARYS provided evidence for TVR with monthly LAN-ATG 120 mg in treatment-naïve acromegalic patients (63% achieved TVR ≥20% with a favourable safety profile). To help clinicians with therapeutic management of acromegaly, tumour responsive over time needs to be further explored.
Methods
PRIMARYS was an international, multicentre, open-label, single-arm study of 90 treatment-naïve acromegalic patients with pituitary macroadenoma receiving primary therapy with LAN-ATG 120 mg every 28 days for 48 weeks. TVR was measured at 12, 24, and 48 weeks on MRI central assessments. The primary endpoint was % of patients with relevant tumour responses (≥20% TVR from baseline) at week 48. Correlation analyses of baseline TV, TVRs at 12 and 24 weeks vs TVR at 48 weeks were performed. Descriptive statistics were used to assess shifts in TVR rates at various time points, and TVR over time stratified by TVR subgroups.
Results
There was a strong and statistically significant correlation between TVR at 12 and 24 vs 48 weeks (correlation coefficient 0.79 and 0.76, respectively; $P<0.0001$ for both). There was no correlation between baseline TV and TVR at 48 weeks. Among patients achieving a tumour response (TVR ≥20%) at 12 and at 24 weeks, the majority maintained a response at 48 weeks (43/46 (93%) and 42/45 (93%) still responders at week 48). In patients with ≥20%TVR at last visit/week 48, the TVR changes at each previous study visit were consistently greater than those in patients with TVR <20% at last visit/week 48 (Fig. 1).
Conclusions
The current analyses suggest tumour responses to primary LAN-ATG 120 mg treatment after 12 and 24 weeks were equally-reliable predictors of tumour response after 48 weeks. The predictive value for longer term tumour response of TVR after only 12 weeks with LAN-ATG may help inform further treatment for an individual patient.

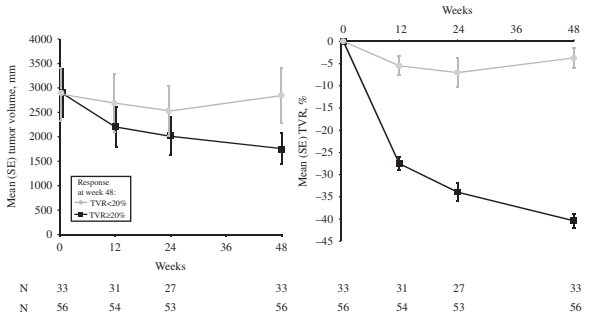

Figure 1 TVR over time in patient subgroups with final TVR ≥20% vs TVR <20%.

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P911

Tumour and hormonal response with lanreotide Autogel 120 mg in treatment-naïve acromegalic patients: further *post hoc* data from the PRIMARYS study

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Introduction
The PRIMARYS study demonstrated primary treatment with lanreotide Autogel 120 mg could achieve favourable tumour and hormone response rates in a large cohort of acromegalic patients. Here, we further interrogate the PRIMARYS database on the relationship between the tumour volume responsiveness and hormonal control.
Methods
PRIMARYS was an international, multicentre, open-label, single-arm study of 90 treatment-naïve acromegalic patients with pituitary macroadenoma receiving primary therapy with lanreotide Autogel 120 mg every 28 days for 48 weeks. Tumour volume reduction (TVR) and hormonal status were measured at 12, 24, and 48 weeks after treatment initiation. The primary endpoint was % of patients with therapeutic tumour response (i.e., ≥20% TVR from baseline) at week 48. Correlation analyses of GH and IGF1 vs TV changes at 48 weeks were performed. Descriptive statistics were used to assess shifts in therapeutic tumour response rates based on hormonal control status at each time point.
Results
Correlation analyses showed that the greater the reduction in GH or IGF1 level, the greater the reduction in tumour volume (correlation coefficients, 0.51 and 0.49, respectively; $P<0.0001$ for both). At each study visit, more patients with hormone control (GH <2.5 ng/ml and normal IGF1) achieved tumour response than those without hormone control (Fig. 1). The TVR response rates did not change greatly over consecutive visits: ranging from 69 to 73% of patients with hormone control, and 41 to 50% of those without hormone control.

Conclusions
These data suggest there is a relationship between tumour and hormone responses to primary lanreotide Autogel 120 mg treatment in acromegalic patients. The data also suggest the relationship may exist as early as 12 weeks and may not necessarily be dependent on longer treatment duration.

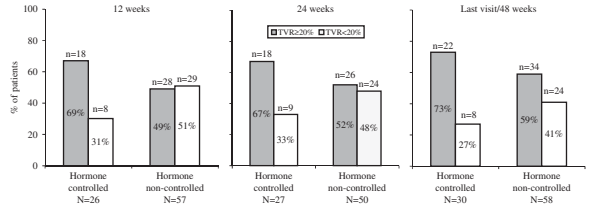

Figure 1 IGF-1 levels (% of ULN) after switching to LAN-ATG EDI during phase 1 and after adjusting/maintaining dose interval during phase 2.

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P912

Efficacy and safety of lanreotide autogel (LAN-ATG) 120 mg at extended dosing intervals (EDIs) in acromegalic patients biochemically controlled with octreotide LAR (OCT-LAR) 10 or 20 mg: The LEAD study

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Introduction
EDIs with LAN-ATG therapy may help improve the burden associated with long-term acromegaly management. The LEAD study evaluated the efficacy and safety of this approach by switching from OCT-LAR conventional dosing to LAN-ATG EDI.
Methods
LEAD was a multinational, multicentre, open-label, non-comparative study. Acromegalic patients with normal IGF1 after OCT-LAR 10 or 20 mg injections every 4 weeks for ≧6 months were switched to LAN-ATG 120 mg at an EDI. In phase 1, patients received five LAN-ATG injections every 6 weeks for 24 weeks. In phase 2, LAN-ATG dose intervals were adjusted/maintained according to IGF1 for another 24 weeks (group A: >100 to $\leq 130\%$ ULN, every 4 weeks; B: >50 to $\leq 100\%$ ULN, every 6 weeks; C: $\leq 50\%$ ULN, every 8 weeks). The primary endpoint was % of patients maintaining normal IGF1 on LAN-ATG EDI of 6 or 8 weeks at week 48. EudraCT:2007-005838-37; ClinicalTrials.gov:NCT00701363.
Results
The ITT population comprised 124 patients who entered phase 1 and received ≧1 dose of treatment (baseline mean age, 54.4 years, time since diagnosis, 8.7 years, OCT-LAR treatment duration, 2.5 years); 109 (88%) entered phase 2 (group A, 12%; B, 64%; C, 24%); and 107 (86%) completed the study. At week 24, 89% (83–94%) of the ITT population maintained normal IGF1 on EDI of 6 weeks. At week 48, 76% (95% CI, 68–83%) maintained normal IGF1 and had EDI of 6 or 8 weeks. IGF1 levels are shown in Figure. Over 48 weeks, treatment-emergent AEs (TEAEs) occurred in 91 (73%) patients; of these, 54 (44%) had treatment-related AEs, and only 8 (7%) had TEAEs leading to study withdrawal. GI disorders were the most common events (39 (32%)).
Conclusions
These data suggest acromegalic patients switching to LAN-ATG could continue IGF1 control without notable safety/tolerability issues; the majority achieved this while benefiting from LAN-ATG EDIs.

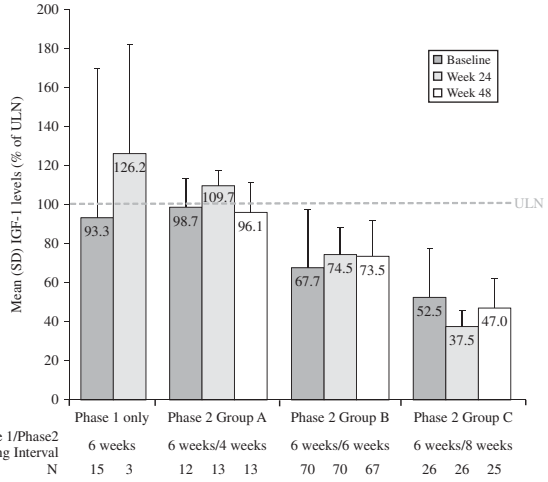

Figure 1 Tumor response in patients with vs without hormone control at each time point.

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P913

Cortisol metabolites response in hypothalamic–pituitary–adrenal axis tests

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The aim of the study was a detailed analysis and a comparison of hypothalamic–pituitary–adrenal axis tests and cortisol metabolites analysis during these tests. This procedure might enable to design new diagnosis algorithms of hypocorticalism and normal levels for salivary cortisol estimation for early diagnostic of patients with hypothalamic–pituitary–adrenal axis disorder as well as to give us a possibility to reveal adrenal disorder in patients on estrogen therapy or with altered levels of cortisol-binding proteins whose hypothalamic–pituitary–adrenal axis evaluation is always problematic.
Sixty healthy volunteers (age 38 ± 10 year (mean $\pm$S.D.), BMI 24.5 ± 2.7 kg/cm^2) were examined by high (250 μg), low dose (1 μg) and 10 μg synacthen test and insulin test (ITT). The study was approved by the local Ethical Committee.
We evaluated serum cortisol, serum cortisone, salivary cortisol, steroids in Δ4 pathway, other steroids and their polar conjugates in Δ4 and Δ5 pathway: reduced 5α/β-metabolites of cortisol during dynamic tests, and basal levels of cortisol binding globulin, aldosterone and ACTH respectively.
All subjects reached the normal response of cortisol (>500 nmol/l) in all tests. The levels of cortisol metabolites were significantly lower in 1 μg synacthen test comparing to remaining tests and the peak was observed at the 60 min after the stimulation. The levels of salivary cortisol were significantly higher 45 ± 4.5 nmol/l in the 250 μg and ITT compared to low and 10 μg synacthen test, 37 ± 2.5 nmol/l.
Conclusion
Four different hypothalamic–pituitary–adrenal axis tests gave similar response of cortisol, however, the response of cortisol metabolites is lower in the low dose synacthen test. These results may contribute to better understanding the pathophysiology of changes in hypothalamic–pituitary–adrenal axis disorders.
The study was supported by grant No. NT11 277-6 of the IGA MZCR.

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P914

Octreotide fluid crystal provides sustained octreotide bioavailability and similar IGF1 suppression to that of octreotide LAR (Sandostatin LAR): randomized, open-label, Phase I, repeat-dose study in healthy volunteers

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Background
Octreotide is the most widely used somatostatin analogue; however, the LAR formulation must be reconstituted prior to intramuscular injection. This Phase I study compared the pharmacokinetics and pharmacodynamics of octreotide Fluid Crystal (FC), a ready-to-use depot formulation for s.c. administration, vs octreotide LAR.
Methods
After a single dose of octreotide s.c. 200 μg, healthy adult male/female volunteers were randomized 1 week later to three injections of octreotide FC 30 mg/month ($n=14$) or octreotide LAR 30 mg/month ($n=14$). Blood samples for octreotide and IGF1 analyses were collected pre- and post-injection, and at pre-specified time points during the study. Adverse events were recorded.
Results
Octreotide FC exhibited a steady, rapid increase to peak concentrations (C_{max}) followed by a slow, exponential decrease through day 28. After injection 3 (steady state): mean ± S.D. $C_{max}=29.3\pm7.1$ ng/ml, mean ± S.D. $AUC_{28d}=3465\pm608$h ng/ml, median (range) $t_{max}=24$ (2–24) h. Octreotide LAR exhibited a burst concentration peak and rapid decline to undetectable values, which rebounded by day 7, stabilized from day 10 and finally decreased around day 21. After injection 3 (steady state): mean ± S.D. $C_{max}=1.8\pm0.6$–ng/ml, mean ± S.D. $AUC_{28d}=733\pm222$h ng/ml, median (range) $t_{max}=1$ (0.5–360) h. Relative bioavailability (using AUC_{28d}) of octreotide FC vs LAR was 487% (90% CI: 411–578). Octreotide FC provided more rapid and greater IGF1 suppression vs octreotide LAR after injection during weeks 1–2, but similar IGF1 levels were seen during weeks 3–4; AUC for IGF1 suppression was similar in both groups. Comparable injection-site and systemic tolerability was seen across both groups.
Conclusions
Octreotide FC provides greater octreotide bioavailability with a more rapid onset and similar duration of effect compared with octreotide LAR in healthy volunteers, and may offer enhanced convenience as medication as it may be supplied in a convenient, prefilled syringe with a thin needle. A Phase III study of octreotide FC in patients with acromegaly is planned.

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P915

Clinical case: Silent corticotroph pituitary macroadenoma transforming into Cushing disease.

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Introduction
The silent corticotropinomas (SC) account for 1.1–6% of surgically removed pituitary adenomas and 17–22% of ACTH-immunoreactive tumours. They do not cause prominent clinical features of hypercortisolism, nor biochemically evident, but show positive immunostaining for ACTH similar to functional corticotropinomas, They usually present as non-functioning adenomas (NFPA) with local mass effects and/or visual impairment.
Aim
To describe the clinical course of a patient operated for NFPA which later in time developed into active Cushing's disease (CD).
Case presentation
The disease presented at the age of 18 years with oligomenorrhea, normal hormonal tests results for TSH, cortisol, LH, FSH, prolactin, and microadenoma 0.8 cm in diameter at MRI. Within a year patient underwent transnasal adenomectomy owing to the rapid suprasellar extension of the lesion at dynamic visualisation. For technical reasons, histological and immunohistochemical analysis was not performed.
At the next follow-up patient complained of persisted oligomenorrhea, the levels of TSH, cortisol, LH, FSH, prolactin remained in normal ranges, there was no data of recurrence on MRI.
At the age 21 years patient presented with clinical signs of CD. Lab data revealed high levels of ACTH/cortisol, absence of significant cortisol suppression at the 1 mg and 8 mg dexamethasone tests. The MRI-scan detected the macroadenoma $1.6\times1.2\times1.0$ cm. The inferior petrosal sinus sampling distinguished pituitary CD. At the age of 21 the patient underwent the second transnasal adenomectomy however adrenal insufficiency did not develop. The immunohistochemical analysis showed ACTH-, LH-, FSH-, PRL-, CgA immunopositivity, negative expression for STH and TSH, ki-67 2%. Because of ineffectiveness of surgical treatment patient was directed to radiation therapy.
Conclusions
This case demonstrates the recurrence and transformation of NFPA into manifested CD during a period of 2 years. The knowledge of the immunostaining characteristics of NFPAs-are important for proper postoperative management.

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P916

Lanreotide-induced bradycardia and supraventricular extrasystoles

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Case
A 63-year-old acromegalic woman admitted hospital for lassitude and dizziness. She has been diagnosed acromegaly 10 years ago and had two transsphenoidal operations. Remission wasn't achieved. Then she started to use lanreotide (somatostatin analogue) and for 7 years she has been treated with it. In laboratory examination, basal plasma GH 1.21 ng/ml (NR:0–5); nadir GH level after glucose tolerance test, 1.2 ng/ml (NR: less than 1); IGF1, 129.1 ng/ml (NR: for age: 75–212); thyroid stimulating hormone (TSH), 0.824 uIU/ml (NR: 0.27–4.2); free thyroxine (fT_4), 1.26 ng/dl (NR: 0.9–1.7); and prolactin, 6.66 ng/ml (NR in women: 0–20). MRI with gadolinium contrast revealed a pituitary microadenoma. Routine resting electrocardiograms of patient showed bradycardia (46 bpm) and supraventicular extrasystoles. Then lanreotide treatment stopped. Patient's symptoms relieved and heart rate increased (64 bpm).
Conclusion
Somatostatin is a peptide hormone with a short half-life (2–3 min), which is synthesized in multiple tissues, including the hypothalamus, to inhibit GH secretion. Somatostatin analogues (octreotide and lanreotide) are indicated principally for the treatment of acromegaly that remains active after transsphenoidal surgery, whether or not the patient has also undergone radiotherapy. Octreotide-induced bradycardia has previously been reported as an unusual finding in different clinical situations (nonacromegalic patients) and a male patient with acromegaly. A rat study shows bilateral microinjection into the rostral ventrolateral medulla of either somatostatin or the receptor-selective agonist lanreotide evoked dramatic, dose-dependent sympathoinhibition, hypotension, and bradycardia. Our case is the first reported patient with acromegaly who had bradycardia and supraventricular extrasystoles associated with use of lanreotide.

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P917

Treating prolactinoma by endoscopic endonasal pituitary surgery: surgical experience of 151 cases

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Background and Aim
Prolactinoma is the most common type of functional pituitary tumor in adults. Giant prolactinomas are defined as tumors achieve a diameter >4 cm and often have very high serum prolactin level. In our previous study showed that endoscopic endonasal pituitary surgery is a very convenient procedure for the patient due to low morbidity and high efficiency. In this study we evaluated endoscopic endonasal pituitary surgery series in patients with prolactinoma.
Methods
We, therefore present a retrospective analysis of the early results of 151 consecutive prolactinoma cases operated by the seniour author (MB) at Hacettepe University, Department of Neurosurgery over a period of 7 years.
Results
A total of 151 patients, 81 (53.3%) female and 70 (46.7%) male, mean age 35.7 ± 13.6 year (range 14–73 year), underwent endoscopic endonasal transspenoidal

surgery for prolactin pituitary tumors. On the basis of MRI data, 21 patients (13.8%) had a microadenoma, 123 (80.9%) had a macroadenoma, and the remaining 8 (5.3%) had a giant adenoma. Cavernous sinus invasion was identified in 23 tumors by MRI, and confirmed by histology ($n=15$). Presenting symptoms included visual disturbance in 22 cases. Pathological diagnosis was atypical adenoma in 14 patients. Immediately after surgery, 34.6% patients went into remission. There were reports of postoperative four CSF leak and third menengitis ın our series. Fifty-five patients needed dopamine agonist treatment post-operatively.

Conclusion

Endoscopic endonasal approach is a safe and effective procedure for the resection of prolactinoma, particularly for the ones which are resistant to dopamine agonists and atypical adenomas. We suggest that tumors with apoplexia, compression to the optic chiasma and invasion to the cavernous sinus are suitable for this type of surgical procedure before considering medical treatment.

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P918

Pharmacokinetic (PK) and pharmacodynamic (PD) analyses of pasireotide LAR and octreotide LAR: Randomized, double-blind Phase III study in patients with medically naïve acromegaly

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Introduction

A recent 12-month randomized, double-blind study showed that pasireotide LAR was superior to octreotide LAR at providing biochemical control (GH and IGF1) in medically naïve patients with acromegaly. This analysis evaluates the PK/PD of pasireotide and octreotide in these patients.

Methods

Patients received pasireotide LAR 40 mg/28 day ($n=176$) or octreotide LAR 20 mg/28 day ($n=182$) for 12 m. The relationship between pasireotide/octreotide concentrations and efficacy (GH and IGF1) was analysed using a non-linear inhibitory E_{max} model and logistic regression models. Exposure and safety (FPG, ECG and liver function parameters) were also evaluated.

Results

Gender, baseline GGT levels and body weight are statistically significant PK covariates for pasireotide, with no clinically meaningful impact on PK exposure; findings were similar for octreotide except for body weight. E_{max} model parameters (Table) show that pasireotide exposure covers the estimated effective concentrations for suppression of GH and IGF1, and pasireotide achieves stronger suppression of IGF1 than octreotide. Octreotide would not achieve normalization of IGF1 even at higher doses. Logistic regression analysis indicated a 36.6% increase in odds of IGF1 normalization with a 50% increase in pasireotide exposure; the corresponding odds increase was only 26.1% for octreotide. The odds of hyperglycaemia occurring increased with pasireotide exposure but to a lesser extent than the odds of clinical response, supporting a positive benefit-to-risk ratio for pasireotide within the dose range tested. There was no clinically significant relationship between exposure to either drug and QTcF/QTcB or liver function parameters.

Table 1 Key model parameters estimated using the non-linear E_{max} model

		GH (mean ± S.E.M.)			IGF1 (mean ± S.E.M.)	
	EC_{50} ng/ml	$C_{effective}$ - ng/ml	Maximum suppression	EC_{50} ng/ml	$C_{effective}$ - ng/ml	Maximum suppression
Pasireotide LAR	0.73 ± 0.16	6.25 ± 1.12	85.31 ± 1.67%	1.84 ± 0.28	13.45 ± 2.39	7358 ± 1.86%
Octreotide UR	0.13 ± 0.02	1.94 ± 0.59	84.05 ± 1.65%	0.22 ± 0.04	NAdueto Insufficient suppression < 1xULN	57 59 ± 2.15%

EC_{50}: half the maximal effective concentration to induce a response on GH or IGF1. $C_{effective}$: the estimated effective concentration for either treatment to suppress G H or IG F1.

Conclusions

PK/PD results support the efficacy analyses; pasireotide LAR has a superior effect on suppressing IGF1 than octreotide LAR. Besides hyperglycaemia, no other safety parameters had relevant associations with pasireotide exposure.

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P919

Copeptin in basal conditions and during water deprivation test in patients with polydipsic–polyuric disorders

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Introduction

Copeptin is a proposed new diagnostic marker in differential diagnosis of diabetes insipidus as it is secreted in equimolar concentrations with vasopressin. Thus our aim was to assess diagnostic value of copeptin evaluation in patients with polydipsic-polyuric disorders.

Materials and Methods

We've evaluated the copeptin (BRAHMS CT-proAVP Kryptor), sodium levels and blood/urine osmolality in 26 healthy volunteers (1M/25F, mean age 24.7 ± 2 years) water deprived for 12 h as well as in 3 patients with central diabetes insipidus (CDI) and 3 patients with primary polydipsia (PP) during water deprivation test.

Results

In 38% (10 patients) of healthy volunteers copeptin level was less than 5 pmol/l (the lower limit of laboratory). The remaining average levels amounted to 8.5 ± 2.8 pmol/l (5.41 to 15.16). In patients with polyuria morning concentrations of copeptin were less than 5, and only one patient who later was diagnosed as CDI were 6.124 pmol/l. After water deprivation till maximum tolerability (4–8 h) patients with PP concentrated urine above 650 mOsm/kg and their copeptin levels increased to 13.59, 16.56, and 11.76 respectively, serum sodium and osmolality were within normal rangers and without any significant changers from basal values. In patients with CDI the levels of copeptin for all were below 5 pmol/l, serum sodium and osmolality increased while urine osmolality remained below 300 mOsm/kg. The Index for stimulated CT-proAVP (the formula provided by assay developer) was 0 for patients with CDI and 60, 81 and 47 for patients with PP (>20 is diagnostic for PP).

Conclusions

Basal copeptin levels in our setting were not helpful for differentiation of healthy people from patients with CDI, but this differentiation was possible with water deprivation test alone with concordant information from copeptin/sodium index calculation.

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P920

A case or recurrent pituitary apoplexy

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A 35-year old female presented with a 5 day history of headache, diplopia and reduced visual acuity preceded by 6 months of lethargy and weight gain. Visual field testing revealed left temporal hemianopia. Magnetic resonance imaging (MRI) showed a benign pituitary adenoma with intra-tumoural haemorrhage compressing the optic chiasm. Neurosurgical opinion advised on transphenoidal surgery. However, in view of spontaneous resolution of diplopia and recovery of peripheral vision, the decision was made to treat the patient conservatively with surveillance MRI scans and neurosurgical follow-up. Endocrine assessment showed pan-hypopituitarism, and the patient was discharged on hydrocortisone and thyroxine. Surveillance MRI scans in 2003 and 2005 showed resolution of the tumour with an enlarged pituitary fossa with a rind of pituitary tissue at the base. Ten years later she represented with sudden headache, decreased vision and right third nerve palsy. Repeat MRI showed recurrence of pituitary macroadenoma expanding the sella turcica and extending to the right cavernous sinus with intralesional haemorrhage in the right sided supracavenous component, confirming the unprecedented recurrence of a pituitary apoplexy. As in the previous episode, her symptoms resolved spontaneously and there was no requirement for surgery. She is currently still under surveillance with the view to undertake a transphenoidal hypophysectomy if indicated clinically or radiologically.

The incidence of pituitary apoplexy is between 5 and 16% in pre-existing pituitary adenomas. We have reported a case of recurrent pituitary apoplexy that was managed conservatively. Recurrent pituitary apoplexy is rarer with no evidence in recent studies to suggest increased incidence of recurrence in conservatively managed patients. The cause of the rare phenomenon of recurrent pituitary apoplexy is not fully understood. The working hypothesis is that of a good vascular supply in younger patients, which makes them prone to recurrent pituitary bleeds.

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P921

Increased prevalence of differentiated thyroid carcinoma in patients with acromegaly

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Background
Acromegaly is associated with increased prevalence of thyroid diseases, particularly of differentiated thyroid carcinoma.
Aim
To assess prevalence of thyroid diseases and thyroid cancer in patients with acromegaly.
Patients and methods
Forty (10 M/30 F) acromegalic patients, 14 residents in iodine deficient areas, aged 47 ± 12.8 years, were retrospectively reviewed. Mean duration of acromegaly was 7.6 ± 9.5 years and median post diagnosis follow-up was 4.1 years. GH, IGF1 were measured by chemiluminescence (Liaison), TSH, FT_4 by immunometric assays (Immulite). Thyroid ultrasonography was performed in all cases, thyroid scintigraphy was performed when indicated; fine needle aspiration biopsy (FNAB) was performed in suspicious nodules, according to current guidelines.
Results
Thyroid abnormalities were present in 28 patients (70%) in our series: diffuse goiter in 8 patients (20%), simple nodular goiter in 5 patients (12.5%), nontoxic multinodular goiter in 10 patients (25%), toxic multinodular goiter in 4 patients (10%), Graves' disease in one patient (2.5%); thyroid carcinoma was found in 3 patients (7.5%). Patients with thyroid nodules larger than 1 cm had significant longer acromegaly duration (6.1 ± 3.6 years) than patients without nodules or nodules less than 1 cm (2.1 ± 1.5 years), $P = 0.008$. Histological type in patients with thyroid carcinoma was follicular variant of papillary thyroid carcinoma in all three cases: 2 microcarcinomas and one macrocarcinoma. All three thyroid carcinomas patients underwent total thyroidectomy and radioiodine treatment (mean cumulative dose 181.7 mCi ^{131}I) and were in stable remission.
Conclusion
Due to increased prevalence of differentiated thyroid carcinoma, active screening for thyroid abnormalities is mandatory both in iodine sufficient and deficient areas, especially in patients with longer duration of acromegaly.

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P922

Oral and dental pathologies in patients with acromegaly

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Introduction
Growth of the tongue and mandible and dental pathologies are recognized consequences of untreated growth hormone excess in acromegaly. However, data on the frequency of the individual oro-dental pathologies are sparse. We, therefore, developed a self-report questionnaire on typical oro-dental changes, therapeutic measures, costs for prosthetic treatment and the role of dental professionals in the diagnostic process of acromegaly.
Methods
The questionnaire was sent out to 320 patients with acromegaly, operated upon between 2000 and 2012. 165 answers were received and analyzed statistically with SPSS. Information on adenoma subtype was provided by the institute of neuropathology.
Results
About 37% of all patients had visited a dentist at any time during the disease process due to oro-dental pathologies. Most frequently, growth of the tongue (54.5%), enlargement of interdental spaces (39.4%), mandibular growth (21.8%) and mandibular prognatism (20%) were reported. 74.9% of the patients suffered from an y oro-dental pathology and 9.6% reported these to be under the first self-noticed symptoms. Seven patients were suspected to have acromegaly by the dentist. The mean self-spent costs for prosthetic treatment amounted to 1,844€ (max. 18,000€). Of those patients with need for dental treatment 42.6% reported a reduction of visits to the dentist after pituitary surgery. 67.9% of the patients with proven acromegaly informed their dentist about their disease. While adenoma subtype had no influence on the occurrence of oro-dental symptoms ($P = 0.816$), their occurrence was significantly lower when acromegaly was diagnosed and treated within 2 years from symptom onset ($P = 0.007$).
Conclusions
Our data show that oro-dental symptoms are frequent in patients with acromegaly and incur frequent visits to dental health care providers. Since most of these symptoms occur during the progressive, untreated course of the disease, we suppose that an earlier diagnosis of acromegaly would reduce oro-dental pathologies and result in lowered health care costs.

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P923

Relationship between growth hormone deficiency and oxidative stress in patients with heart failure: Preliminary data.

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It is well known that heart failure is associated with oxidative stress (OS). Reactive oxygen species in fact influence sarcolemmal and mitochondrial ione channels, which are responsible for cardiomyocyte excitability and are important in myocardial remodeling after a myocardial infarction. The decrease of anabolic axes can have a role in the progression of the illness.
In order to evaluate the relationship between growth hormone deficiency (GHD) and indexes of OS, we have performed a dynamic GH evaluation and determined oxidized form of coenzyme Q_{10} (CoQ_{10}) (component of mitochondrial respiratory chain also endowed with antioxidant properties) in a group of 12 patients (10 male and 2 female, age 49–73) affected by heart failure (NYHA II-III; EF < 40%).
GH secretion was evaluated after administration of Arginine (20 g/500 ml) + GHRH (50 μg). Basal IGF1 was also assayed. GH was evaluated by CLIA method, IGF1 by ECLIA and CoQ10 was evaluated by HPLC, as total and oxidized form, also calculating their ratio (CoQ_{ox}/CoQ_{tot} ratio).
Five out of 12 patients presented a total GHD (mean ± ES peak GH: 3.87 ± 2.73 ng/ml; IGF1: 97.4 ± 9.8 ng/ml). 3 showed a partial GHD (mean ± ES peak GH: 8.98 ± 2.94 ng/ml; IGF1: 143 ± 57.21 ng/ml). While 4 patients showed a normal GH response (mean ± ES peak GH: 16.05 ± 0.88 ng/ml; IGF1: 122.5 ± 24 ng/ml).
CoQ_{ox}/CoQ_{tot} ratio were significantly higher in GHD patients (mean ± ES 14 ± 0.04%) than in patients with normal GH (mean ± ES 7 ± 0.01%), thus expressing an augmented oxidation of the molecule.
These preliminary data indicate that GHD is associated to an increased OS in patients with heart failure and suggest that this hormonal alteration can have a role in the physiopathology of this condition.

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P924

GH Deficiency in HIV-infected patients compared to hypopituitary patients

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Introduction
Growth Hormone deficiency (GHD) is frequent in patients with human immunodeficiency virus 1 (HIV-1), undergoing highly active antiretroviral therapy. GHD seems to depend on HIV-related lipodystrophy and to be less frequent in women.

Aim of the study
To investigate the association of gender, body composition and GH/IGF1 axis, and to clarify whether GHD in HIV-infected patients is functional or a clinical entity.
Methods
We compared 47 HIV-infected patients prospectively enrolled, with 36 hypopituitary subjects retrospectively selected reviewing record charts. We evaluated basal serum GH, IGF1, GH peak and area under the curve (AUC) after standard GH Releasing Hormone + Arginine test; BMI, waist and hip circumference and body composition by dual-energy X-ray absorptiometry (DEXA). Data were analyzed by nonparametric Mann–Whitney test.
Results
HIV-infected patients had higher GH peak, AUC, and IGF1 ($P<0.0001$). BMI ($P=0.003$), total ($P<0.0001$) and trunk fat mass ($P=0.0003$) were higher in hypopituitary patients; waist to hip ratio (WHR) was higher in HIV-infected patients ($P<0.0001$). GH peak was lower in hypopituitary men than women ($P=0.001$). Men showed higher WHR ($P=0.0082$), total ($P=0.0002$) and trunk lean mass ($P=0.0008$), while women had higher total ($P=0.0017$) and trunk fat mass ($P=0.0176$). No gender differences were found in HIV-infected patients. GH peak, AUC, and IGF1 were higher ($P<0.0001$) in HIV-infected than hypopituitary men. No difference was found in women.
Conclusions
GHD seems to be worse in hypopituitary patients, suggesting that primary pituitary disease affects GH/IGF1 axis more than HIV-1. Moreover, fat distribution more than fat mass per se seems to affect GH/IGF1 axis in HIV-infected patients, since they have lower BMI but higher WHR. Furthermore, men seem to have a worse deficit than women, suggesting a possible role of gender in GH/IGF1 status. These differences could help distinguishing functional from clinical GHD in HIV-infected subjects, and better targeting treatment strategies.
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P925

Conservative management of pituitary apoplexy – own experience
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Introduction
Pituitary apoplexy is a life-threatening entity developing as a result of ischemia or hemorrhage into pre-existing pituitary tumor. Clinical course is characteristic and commonly consists of severe headache accompanied by nausea, emesis, impaired consciousness, visual field impairment as well as eyeballs movement restriction. Symptoms are typically accompanied by secondary adrenal insufficiency. Corticosteroids are drugs of choice regarding coexisting adrenal insufficiency. In case of a lack of expected both general and neurological improvement during conservative treatment, a surgery might be necessary. Prognosis in case of a proper treatment is good.
Aim of the study was prospective evaluation of the results of conservative treatment of pituitary apoplexy.
Material and methods
The analysis of seven patients (three women and four men) with diagnosed pituitary apoplexy. Median age was 54 years old (range: 23 to 74 years). All patients had endocrinological, ophthalmological and radiological assessment performed before treatment as well as in the follow-up period.
Results
There were no fatal complications. Initial and distant hormonal assessment revealed impairment of the anterior lobe of pituitary. In no cases diabetes insipidus had been reported. During conservative treatment the visual field improved as well as withdrawal of pre-existing paresis of ocular nerves were obtained.
Conclusions
Conservative treatment is a safe method of pituitary apoplexy's management.
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P926

Pituitary apoplexy: surgical or conservative management
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Objectives
The rarity of pituitary apoplexy renders it a difficult subject for audit; hence there are no evidence-based standards of optimum care for such patients. The main controversy in management relates to the role of acute surgical intervention. Recently, a more conservative management has been adopted towards patients presenting with this condition. Therefore, it is important to evaluate the differences in outcome between patients submitted to surgical and conservative management.
Methods
A retrospective analysis was performed to evaluate all patients that presented with pituitary apoplexy since 1998 were followed in Hospital de Braga. Clinical presentation, management, and clinical outcomes were evaluated. We then performed a descriptive statistical analysis. Student's *t*-test and Pearson's χ^2 test or Fisher's exact test were used for comparing between groups. We admitted a P value <0.05 to be statistically significant.
Results
There are no statistically significant differences in outcome between the patients that had surgery and the patients that followed conservative management, ($\chi^2(1)=0.002$; $P=0.967$; $n=50$). Differences of statistical significance were found between the 2 groups in the following data: on average, the operated tumors are 11.67 mm bigger than the ones in patients with conservative management, ($t(48)=4.925$, $P<0.001$, $d=1.375$, $r^2=0.32$); there are also differences in para-selar extension, ($\chi^2(4)=16.554$; $P=0.001$; $n=50$), and infra-selar extension, ($\chi^2(2)=7.935$; $P=0.013$; $n=50$), with a bigger concentration of significant results in Knosp 1 and Knosp 3. The surgical group also presented a bigger concentration of growth into the sphenoidal sinus, (Adjusted Standardized Residuals $>|1,96|$).
Conclusion
The conservative management should be considered, without presenting an increased risk for the patients, regardless of clinical presentation, visual deficits, or endocrinal deficits during admission. However, we do recommend that patients presenting with tendentially larger tumor diameter or Knosp should be evaluated on a case-by-case basis in order to determine the best acute management.
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P927

Histiocytosis of pituitary gland: a case report
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Histiocytosis is a disease caused by growth of histiocytes within one or more organs. Symptomatology may be very different: from isolated skin or bone lesions, by diabetes insipidus after life-threatening multisystem form. Diabetes insipidus as a symptom of pituitary can be observed many years before visibility of the changes in magnetic resonance imaging.
A case of 59-year-old woman who has experienced diabetes insipidus with no other symptoms of hypopituitarism is presented in this study. It was the only symptom of the disease. She felt very well and she didn't receive any medical treatment. Increased level of OB, LDH, and decreased urine specific gravity were found in the laboratory tests. MRI of the pituitary revealed infiltration of the hypothalamic- pituitary area. Extensive diagnostics was conducted to be sure that inflammatory didn't cause the infiltration. During this process, the presence of numerous, multiorgan changes (numerous small focal lesions in the lung, gallbladder, and ovaries) was revealed. Because of polyuria she received desmopressin.
The most nagging discomfort the patient felt in the right ear. The ENT consultation revealed a change resulting in narrowing of the external auditory canal. The change within the right temporal bone was described during the CT of the head. Material collected for histopathological examination during surgery allowed for the diagnosis: eosinophilic granuloma. The inflammatory infiltration was composed of lymphocytes and many histiocytes.
Owing to the high risk of complications, pituitary gland biopsy is not performed. After inflammatory infiltration of the pituitary was excluded, histiocytosis of the pituitary was recognized. The diagnose of the systemic histiocytosis was performed and the patient was sent to chemotherapy.
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P928

Diabetes inspidus post traumatic head injury

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Background
Cranial diabetes inspidus (DI) may be familial or acquired. Traumatic brain injury is an important cause of acquired cranial DI, occurring in up to 22% of patients with moderate or severe head injuries[1].
Case 1
A 20-year-old male was admitted following a road traffic accident (RTA) with polytrauma including several skull fractures, subdural haematoma, and pneumocephalus. The following day, he developed polyuria and polydipsia. Biochemistry was suggestive of DI (serum osmolality-301 mOsm/kg, Serum Na 141, urine osmolality 86 mOsm/kg, urine Na- <10 mmol/l). He was managed conservatively for his neurosurgical injuries, but underwent intervention for a comminuted mandibular fracture. He was started on oral desmopressin 100 μg mane and 200 μg nocte with good clinical response. Anterior pituitary function was normal. At 6 months, he is well and off desmopressin.
Case 2
A 23-year-old male presented with a 4 week history of polydipsia and polyuria which started within 24 h of RTA. He had a small intracranial bleed but required no surgical intervention. He had mild hypernatraemia(147 mmol/l) with an elevated serum osmolality (303 mOsm/kg) and inappropriately low urine osmolality (70 mOsm/kg). Calcium, potassium, glucose, and anterior pituitary function tests were normal. His symptoms and biochemistry normalised rapidly after a dose of Desmopressin. MRI pituitary showed loss of the posterior pituitary bright spot. He was started on desmopressin nasal spray 10 μg morning and 20 μg night time. He remains asymptomatic on same dose of Desmopressin at 18 months post head injury.
Discussion
Both syndrome of inappropriate ADH and DI are common immediately post head injury. Most of these patients recover, however a small but significant number (6.9%) are left with permanent DI[1]. Water intake may be inadequate in the early post head injury period due to impaired cognition, physical disability, or coexisting hypodipsia with potentially serious consequences[1]. In contrast to DI, anterior pituitary hormone deficiencies may develop many years after head injury[2].
Reference
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P929

Malignancies in patients with pituitary adenomas

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Abstract
Pituitary adenomas (PA) may occur in association with malignancies. Although an increased risk of cancer has been reported in acromegalics, this has been poorly studied in patients with other phenotypes. We wished to evaluate the prevalence of recognized malignancies in PA.
Material and Methods
A series of 422 consecutive PA patients followed at the Neuromed Institute between 2006 and 2012 was retrospectively reviewed and analysed. Data were compared with the Italian registry of tumours.
Results
Patients (289 F, 133 M) were affected by PRL-(223), GH-(52), ACTH- (19) and non-functioning (128) PA. Malignancies were recorded in 25 patients (5.9%, 13F, 12M) with a significant difference according to the PA phenotype ($P=0.015$): the highest prevalence was observed in patients affected by NFPA (14/128, 10.9%), followed by GH and PRL-secreting PA (4/52, 7.7% and 7/211, 3.1%,respectively) . The overall prevalence of cancer was not significantly higher than in the Italian population (4.6%, Pns), except for patients with NFPA (Chi-2 $=9.05$, $P=0.003$). Fourteen different types of malignancies were recorded, including four papillary thyroid cancer, four bronchial cancer, four prostate cancer (three NFPA patients and one acromegalic for each type). Only two breast and two colon cancers were observed (one NFPA and one prolactinoma for each type). Cancer patients were older than other patients (53.0 ± 15.1 *vs* 38.5 ± 16.1 years-old, $P<0.001$), and among them men tended to be older than women (57.4 ± 17.0 *vs* 49.3 ± 12.9 years, $P=0.109$). Two patients developed more than one malignancy.
Conclusion
Patients with NFPA may be at higher risk of cancer than previously reported, and this should be taken in mind during the follow-up of such patients. The absence of colon cancer in this series of acromegalics suggests that improvements in disease control and resection of colonic polyps are efficiently reducing the risk in these patients.

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P930

Psychosocial changes in patients with acromegaly: the preliminary results

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Objective
The cross-sectional study was designed to assess the psychosocial profiles of patients with acromegaly and with non-functioning adenomas in correlation with the severity of the diseases.
Methods
Forty-one patients with acromegaly and thirty-one with non-functioning adenomas underwent a cross-sectional assessment regarding their socio-demographic and medical profiles, including the quality of life, psychiatric morbidity, and acceptance of illness. Patients with acromegaly were divided into three subgroups accordingly to minimal GH concentration during the OGTT and IGF1 concentration: cured acromegaly group, well-controled acromegalic group, and active acromegaly group.
Results
The acromegaly group in total had mean age 52.31 ± 14.81, and mean duration of illness since diagnosis of 8.71 ± 8.69 years. The average ACROQOL score was 55.38 ± 16.33, with the mean physical dimension score of 53.05 ± 20.70 and mean psychological dimension of 56.72 ± 15.73. Age, quality of life and acceptance of illness were factors not associated in acromegaly vs non-functioning adenomas comparison. About 40.48% of acromegaly patients and 53.13% of non-functioning adenomas patients scored positive indicating presence of psychiatric morbidity on the GHQ-28. Compared to the GHQ-negative group in all subjects, the GHQ-positive group had significantly poorer quality of life in physical health domain measured with WHO Quality of Life- BREF ($P<0.001$) and lower scores in AIS scale ($P<0.01$). Further statistical analyses groups divided by severity and progress of the disease are currently performed and will be presented at the congress.
Conclusion
Results of the study indicated that patients with pituitary adenomas may have mental co-morbidities and psychosocial problems. The coexistence of mental disease disorder may have impact on the quality of life, as well as on the acceptance of illness depends and activity of the disease.

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P931

Population-based cohort study: *PROP1* gene mutations are the most prevalent cause of congenital multiple pituitary hormone deficiency in Lithuania

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Introduction
Congenital multiple pituitary hormone deficiency (MPHD) may result from defects of transcription factors that govern the early pituitary development. The most prevalent are two mutation of *PROP1* gene: the c.296delGA and c.150delA.

Methods
Seventy-five Lithuanian MPHD patients were tested for *PROP1* defects. Perinatal and postnatal data were obtained from medical records. Hormonal investigations, pituitary imaging and GH therapy were performed at a single centre in Kaunas. The *PROP1* gene was investigated by Sanger sequencing. Ancestral origin of mutation was assessed by genotyping of 22 single nucleotide polymorphisms flanking the *PROP1* gene, and their haplotype analysis.
Results
Fifty-two subjects (69.3%; 28 males; including ten sibling pairs and two sibling triples) from 38 families were found to carry a biallelic *PROP1* gene mutation. Fifty of these were homozygous 296delGA and two were compound heterozygotes 296delGA/R71H and 296delGA/150delA. We found the highest rate of *PROP1* mutations among MPHD patients from populations studied so far (17.5 per million).
Patients' birth lengths/weights were normal. Height declined to S.D. −1.56, −2.34, −3.43, −3.52, and −3.70 (medians) at years 1–5. Deficiencies of GH, TSH, ACTH, and FSH/LH were diagnosed in 50/52, 52/52, 21/52, and 25/52 subjects at median age 5.5; 5.6; 13.1, and 15.0 years respectively. Pituitary height ranged from 16.6 (+20.2 S.D.) to 1.4 mm (−15.5 S.D.) and declined with age ($r^2=0.27$, $P=0.001$). GH therapy increased growth rates to 12.2; 9.1; 6.9; 6.8; 6.7; 5.6, and 5.7 cm/year (medians).
The mutation carriers were found to share a common ancestor with the c.296delGA mutation having arisen about 112 generations ago ($P \leq 3 \times 10^{-4}$).
Conclusions
The population-based cohort of patients with *PROP1* gene mutation is the largest described so far. High prevalence of *PROP1* defects in Lithuania is due to a founder effect of c.296delGA mutation.

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P932

Cabergoline-induced pneumocephalus: an unusual complication of macroprolactinoma treatment

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Prolactinomas are the most common hormonally active tumours of the pituitary. The treatment of choice is pharmacological. They are treated with cabergolin, which decreases the level of prolactin as well as the size of the tumour. Rarely, dangerous complications can arise after a quick reduction of the tumour's size.
Case presentation
Two men with macroprolactinomas were initially treated with cabergoline (Dostinex®) in a dose of 1 mg per week with increase to 2 mg per week after 7 days of treatment. Six to seven weeks after the initiation of treatment, rhinorrhea appeared in both patients. The first patient experienced headaches and a worsening of ocular perimeter on the right side. Cranial computed tomography scans showed pneumocephalus in both patients. In the first patient, there were no findings of cranionasal communication on cisternography. After withdrawal of cabergoline, the pneumocephalus had gradually reduced in size. In the second patient, two endoscopic transsphenoidal repairs of the defect were performed as well as tumour debulking. After the surgery cabergoline was once again started in lower doses for visual field defects.
Conclusion
Pneumocephalus is a rare complication in pharmacologically treated macroprolactinomas. Quick diagnosis and urgent surgical treatment are of utmost importance.

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P933

An unusual cause of hypopituitarism

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A 64-year-old Sri Lankan female was admitted with a 1 week history of vomiting and poor oral intake. She had an episode of pneumonia 4 months previously and reported headaches, weight loss and dizziness since then.
On admission, her blood tests showed marked hyponatraemia with a sodium of 118 mmol/l and low serum osmolality of 243 mOsm/kg. A short synacthen test confirmed adrenal insufficiency and thyroid function tests showed secondary hypothyroidism despite being on levothyroxine for previously diagnosed hypothyroidism (TSH, 0.2 mU/l and Free T4, 7.1 pmol/l). Her prolactin and IGF1 levels were normal. Her gonadotrophins were low for a post-menopausal female (LH- 0.7 IU/l, FSH- 8.4 IU/l).
She was started on hydrocortisone, followed by up-titration of her levothyroxine which improved her symptoms and biochemistry.
She underwent an MRI pituitary; this showed the gland to be normal in size/structure, however, the pituitary appeared bright. A subsequent CT Brain/Pituitary showed small plaques of dural calcification which were within normal limits; there were no signs of calcification of the pituitary or brain substance. Other investigations, including a CT Thorax for possible granulomatous disease proved unremarkable.
Manganese is a paramagnetic substance; given the hyperintensity seen on MRI we were advised to check manganese levels. Interestingly, this was elevated at 391.5 nmol/l (RR: 72.8 – 218.5 nmol/l), suggesting hypopituitarism secondary to manganese toxicity.
Discussion
Heavy metal toxicity is a rare cause of neurological disorders and an even rarer cause of pituitary dysfunction, with the exception of iron. Classically, manganese toxicity causes features resembling Parkinson's disease and arises from environmental/industrial overexposure, and is seen more commonly in groups such as miners and welders. Contaminated water wells and haemodialysis are also recognised causes. Much is yet to be understood about manganese homeostasis and toxicity; we present a case of hypopituitarism, a feature that has not previously been described in literature.

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P934

Russian registry of patients with tumors of the hypothalamic-pituitary region (OGGO): October 2013 update for acromegaly

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Introduction
The Russian Registry of patients with tumors of the hypothalamic–pituitary region (OGGO) is a national registry founded in 2004 by Russian society for Endocrinology and Endocrinology Research Centre as a patient registry for acromegaly, in 2006 it was expanded to collect information on all lesions of the hypothalamic–pituitary region, in 2010 the first fully electronic version and in 2013 a new upgraded electronic online version were implemented. At this point the Registry is actively supported by 22 out of 83 regions of Russia, representing about 1/3 of population.
Materials and methods
There are overall 5340 patients registered in the OGGO from 2004 to 2013.
Results
The largest part of registered patients constitutes patients with acromegaly (53%), followed by patients with prolactinomas (26%), inactive pituitary tumors (9%), Cushing's disease (6%), mixed secretion pituitary tumors (4%), and other tumors (2%). Among 2781 patients with acromegaly 72% are women. Peak incidence is between the ages of 40–50 years. 1% of patients have got first (highest) degree of disability, 18% - second degree and 13% - third degree. 57% of acromegalic patients do not have updated disease status, only 6% of patients have remission, 7% partial remission and 30% are in the active state of the disease. Hypopituitarism is present in 9% of patients, visual disturbances in 16% and neurologic complications in 63% (e.g. headaches – 87.5%, carpal tunnel syndrome – 5%, ptosis – 3.7%, vertigo – 2.7%, diplopia – 0.9%). Surgery was performed in 33.1% of patients, 17% received radiation therapy and 49% - drug therapy (octreotide long acting – 28%, lanreotide long acting – 2.6%, bromocriptine – 24%, cabergoline – 5.6%, with about 9% of patients receiving combination therapy of dopamine agonists and somatostatin analogs).
Conclusions
Acromegaly is a highly disabling disease. Our database show low implementation of surgical and specific drug treatment among acromegalic patients.

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P935

Prevalence of thyroid dysfunction in naïve acromegalic patients

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Introduction
Thyroid diseases are frequent in acromegalic patients. We aimed to investigate thyroid function and morphology in a population of patients with *de novo* acromegaly.
Materials and methods
We evaluated 32 patients newly diagnosed with acromegaly in a single medical center. We collected data on patient's age, sex, duration of acromegaly symptoms, history of thyroid disease, laboratory tests results (serum GH, IGF1, TSH, fT4, fT3, and antithyroid antibodies), thyroid ultrasound (US), and fine-needle aspiration biopsy (FNAB) results and treatment applied in patients with thyroid diseases.
Results
In the studied group of 17 female and 15 male acromegalic patients with mean age of 51.3 ± 12.7 years and mean disease duration of 10.4 ± 5.4 years, thyroid disorders were found in 27 cases (84.4%). Eighteen patients were diagnosed with thyroid disease on admission and nine patients had a history of thyroid disease and prior treatment (among them two had thyroidectomies: one for papillary carcinoma and one for multinodular goiter (MNG); two patients were treated with thiamazole for toxic MNG and 1 with L-thyroxine for autoimmune hypothyroidism). Together, 14 individuals (43.8%) had thyroid dysfunction: 8 (25%) subclinical and 3 (9.4%) overt hyperthyroidism and 3 patients (9.4%) hypothyroidism. Median thyroid gland volume was 30.81 ml (range: 10.4–191.4) and we found enlarged thyroid gland in 12 women (80%) and in 9 men (64.3%). MNG was the most frequent US finding ($n = 20$, 66.7%). FNAB was performed in 14 patients. In one male patient a new papillary carcinoma was diagnosed and subsequently he was treated with thyroidectomy and radioiodine ablation. Nine patients underwent radioactive iodine treatment.
Conclusion
We found a high frequency of thyroid dysfunction especially subclinical hyperthyroidism and high prevalence of nodular thyroid disorder in a population of naïve active acromegalics. We suggest routine screening for thyroid diseases in all patients with newly diagnosed acromegaly.

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P936

Dilated cardiomiopathy and acromegaly

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Introduction
Chronic somatotropin (ST) hypersecretion has systemic effects. It can cause important structural and functional cardiovascular (CV) changes, which can result in increased morbidity and mortality.
Case report
A 48-year-old, male. followed by cardiology since 2005 for dilated cardiomyopathy (DCM) (Ecocardiography: moderately dilated left ventricle with globular appearance. Severely impaired global systolic function - LVEF 25%. Right cavities not dilated. Slight thickening of the interventricular septum. No morphologic valvular alterations) after detection of complete left bundle branch block (LBBB) on an ECG performed during preoperative evaluation for varicose vein surgery. Since that time, he also referred increased size of hands/feet and prominence of the forehead. In 2010, he was diagnosed acromegaly caused by a pituitary adenoma (Immunohistochemistry: ST expression and less of prolactin). It was performed transsphenoidal resection, but it wasn't achieved biochemical control even with medical treatment. He also presented evidence of residual disease on pituitary magnetic resonance, motivating a second surgery in 2012. Then he restarted octreotide LAR with biochemical control. In the postoperative period, he presented epigastric discomfort associated with widespread changes on ECG ST segment. It was performed cardiac catheterization, but no significant obstructive lesions were found. He had already done a myocardial perfusion scintigraphy which was negative for ischemia. These two procedures allowed the exclusion of coronary arterial disease. He maintain follow-up with cardiology and at the evaluation in 2013 he presented an LVEF 20% with intra/interventricular asynchrony and a LBBB on ECG with QRS complex duration of 190 msec. Given this, a cardiac resynchronization device was implanted.
Discussion
Although rare, DCM is possible in the evolution of acromegaly. In some cases there may be improvement of cardiac dysfunction and structural changes with somatotropin normalization. However, in others cases specific treatments are needed to reduce the associated CV morbidity and mortality.

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P937

IGF1 response to rhGH in adult GHD: role of GH receptor (GHR) isoforms

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The IGF1 response to recombinant human growth hormone (rhGH) showed some individual variability and the responsible factors for this behavior remain unknown. Some studies have emphasized the possible role of isoforms of the GH receptor (GHR), showing conflicting results.
Therefore, we investigated the possible influence of the isoforms of the GHR to the diagnosis of GHD and in determining adult hormone replacement therapy responsiveness.
We studied 69 patients with GHD (M: 37, F: 32, mean age 40.9, median age 41) treated with rhGH using an identical standardized protocol in a single centre, with a duration of follow-up (median) up to 60 months.
We have observed that there is no significant difference in terms of IGF1 and GH peak at diagnosis of GHD, while the presence of the d3-GHR in homozygosity is related to a significant increase in IGF1 levels at 6 and 12 months of therapy; main determinants of the increase of IGF1 at both 6 and 12 months appear to be the dose of rhGH, the patient's age at diagnosis and the genotype of the GH receptor. No differences between genotypes were found in the long-term follow-up.
GHR isoforms seem to affect the IGF1 response to rhGH in short term follow-up, but further prospective studies will clarify whether this hypothesis may have a predominant role in the variability of patient response to hormone replacement therapy.

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P938

Markers of proliferation and invasion in somatotropinomas

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Introduction
In the search for markers of invasiveness of pituitary adenomas, we studied the expression of Ki-67 antigen, TOPO 2A (topoisomerase 2 alpha), AIP (Aryl Hydrocarbon Receptor-Interacting Protein), and VEGF (Vascular Endothelial Growth Factor) in somatotropinomas.
Material and methods
We studied retrospectively a group of 31 patients (20 female, 11 male) of mean age 43.3 ± 14.3 years who underwent pituitary tumour surgery. Expression of

Ki-67, TOPO 2A, AIP, and VEGF in surgical specimens was determined by immunocytochemistry. Relations between quantitatively determined staining indices and clinical symptoms, tumour features, and MR imaging, were analysed. In all studied adenomas GH expression was confirmed by immunostaining. The mean value of the largest tumour dimensions in MRI, was 22.84±21.23 mm. Local invasiveness, defined as sella turcica destruction, cavernous sinus penetration, optic chiasm compression or suprasellar propagation, was observed in 18/31 patients (58.1%).
Results
In our somatotropinoma samples, Ki-67 was expressed in 77.4%, TOPO 2a in 87.1%, AIP in 83.8%, and VEGF in 87.1% of 31 cases. The median values of Ki-67, TOPO 2a, AIP, and cytoplasmic VEGF indices were 1.23% (IQR=2.17), 1.5% (IQR=1.6), 21.16% (IQR=19.76) and 16.64% (IQR=16.41) respectively. Ki-67, TOPO 2a, AIP, and VEGF indices did not correlate with patient age nor gender ($P>0.05$). Values of Ki-67 and of TOPO 2A indices correlated with tumour size (for Ki-67: $r=0.42$, $P=0.025$; for TOPO 2A: $r=0.53$, $P=0.003$). No correlation between AIP or VEGF expression with tumour size was found. In invasive, as compared with non-invasive somatotropinomas, significantly higher indices were found only for TOPO 2A (median values: 1.96% (IQR=1.9) vs 1.04% (IQR=1.4), $P=0.034$).
Conclusions
Ki-67, TOPO 2a, AIP, and VEGF were expressed in over 70% of all somatotropinomas. Only Ki=67 and TOPO 2A expression was related to tumour size. Only TOPO 2A expression was found to correlate with tumour invasiveness.

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P939

Individual risk factors of metabolic syndrome in adult patients with GH deficiency: a cross-sectional case-control study

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Metabolic abnormalities in adult GH deficiency (AGHD) determine its significance as a disease associated with increased cardiovascular risk. However, recent contradictory data about the long-term beneficial effects of GH replacement, especially on cardiovascular risk, provoked some further analysis of its contributory factors.
Aim of the study
To identify the individual risk factors of metabolic syndrome (MS) in AGHD and to compare the prevalence and the characteristics of MS in a cohort of GHD patients with age- and sex-adjusted control group.
Material and methods
Individual risk factors of MS were evaluated in 54 adult patients with GHD (COGHD: $n=19$, AOGHD: $n=35$) and in age- and sex-adjusted control group of 2153 subjects participating in Bulgarian population-based study of thyroid diseases and diabetes mellitus. GHD was diagnosed according to the Endocrine Society Clinical Practice Guideline recommendations from 2011 and MS was scored by the NCEP-ATP III definition.
Results
The main metabolic abnormalities in GHD group were increased waist circumference (50.0%), low HDL-cholesterol (42.6%) and hypertriglyceridemia (40.7%). Moreover, their prevalence was significantly higher than in control group ($P=0.013$, $P=0.019$, and $P=0.010$ respectively). Only the prevalence of increased blood pressure was significantly higher in control group ($P<0.0001$). However, the difference in MS prevalence among GHD patients (29.6%) and control subjects (24.9%) failed to reach statistical significance ($P=0.429$). Among patients in both groups, already diagnosed with MS, increased blood pressure was the only component which prevalence remained significantly different ($P=0.002$).
Conclusion
AGHD is associated with the development of visceral obesity and dyslipidemia. Nevertheless, these adverse cardiovascular risk factors did not determine a higher prevalence of metabolic syndrome in GHD patients compared to control subjects. These results, as well as recent controversial data about long-term effects of GH replacement therapy on cardiovascular risk, face endocrinologists with the necessity of strict selection of patients initiating GH substitution and of the appropriate duration of this treatment.

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P940

Assessment of glucose homeostasis alterations, inflammatory markers, and coagulation parameters following a successful transsphenoidal surgery for Cushing's disease: preliminary report.

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Background
Cortisol excess in Cushing's disease (CD) leads to metabolic complications, thromboembolic events, and increased cardiovascular risk. The aim of this study was to assess the reversibility of glucose homeostasis alterations and dynamics of inflammatory and coagulation parameters following the successful transsphenoidal surgery.
Methods
The group consisted of 14 patients with CD (11 females; age: 41.5±14.5) operated on according to the same protocol. 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 surgery. HOMA–IR, QUICKI, and Matsuda indices were calculated. Patients previously diagnosed with diabetes were assessed exclusively for fasting glucose and HbA1c.
Results
Three patients (21.4%) had been diagnosed with diabetes prior to CD confirmation. Three patients (21.4%) were diagnosed with diabetes based on OGTT results prior to surgery. Six patients (42.8%) were diagnosed with impaired glucose tolerance. Three months after the surgery, significant reduction in waist (119.7±15.5 vs 114.7±14.7 cm, $P<0.001$) and hip (113.8±14.8 vs 109.1±12.4 cm, $P<0.05$) circumference was observed. A significant decrease in OGTT parameters was confirmed: mean blood glucose (159.3±35.9 vs 123.4±22.8 mg/dl, $P<0.05$), 120-min blood glucose (170±58 *vs* 128.6±39.8 mg/dl, $P<0.05$), and 90-min insulin (205.5±115.8 vs 122.6±100.2 μIU/ml, $P<0.05$). The Matsuda index improved significantly (1.76±1.0 vs 3.4±2.2, $P<0.05$). No differences were observed in BMI, mean and fasting insulin levels, HbA1c, HOMA-IR and QUICKI, hsCRP, D-dimers and fibrinogen.
Conclusion
Three months following successful surgical treatment of CD significant improvements in waist and hip circumference as well as a decrease in mean OGTT glucose levels could already be seen. The Matsuda index, which is based on mean OGTT glucose and insulin levels, might be the most sensitive out of IR indices in the early postoperative period. To demonstrate differences in insulin levels during OGTT, inflammatory and coagulation parameters, a longer follow-up may be required.

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P941

Determinants of survival in treated patients with acromegaly

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Introduction
Patients with untreated acromegaly have a reduced survival, mostly due to vascular disease. Recent studies claim an improvement of survival in the last years.
Aims
To assess mortality ratio and to identify prognostic factors associated with reduced survival in acromegaly.
Methods
Three hundred and twenty-seven patients (207 F/110 M, mean age 48.1±0.7 years, (range 18–81.42)) with acromegaly admitted in a single Neuroendocrinology Department between January 2001 and December 2012 were retrospectively studied by GH, IGF1 levels at diagnosis and posttreatment, therapy, pituitary failure, date and cause of death. PAMCOMP computation program was used to calculate standardized mortality ratio (SMR). Cox regression analysis revealed independent factors associated with mortality. Serum GH levels were measured by IRMA (sensitivity 0.1 ng/ml).

Results
Crude death rate was 11.2 deaths/1000 person years, with an average follow-up of 1963.2 person years (median −5.9 years). All causes mortality rate was not statistically different from that of general population: SMR was 1.06 (95% CI 0.69–1.7).
Survivors were more frequently treated by pituitary surgery (202/305 patients), and/or somatostatin analogues (125/305 patients) than deceased patients (8/22 received operation, $P=0.04$ and 2/22 received somatostatin analogues, $P=0.04$). Posttreatment GH levels (hazard ratio (HR) 1.06, 95%CI 1.03–1.09), acromegaly duration (HR 1.08, 95%CI 1.02–1.1) and age at diagnosis (HR 1.06, 95% CI 1.02–1.1) were independent predictors of mortality. Posttreatment GH levels above 5.5 ng/ml was associated with an increased mortality: SMR = 1.7 (95%CI 1.003–2.853).
Conclusions
Patients with acromegaly admitted in the last 12 years had a mortality rate similar with general population, mainly due to modern therapy. Posttreatment serum GH levels and acromegaly duration were the main predictors of survival.

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P942

Surgical treatment of ACTH-secreting pituitary adenomas in nelson syndrome

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Nelson's syndrome (NS) is a rare clinical syndrome of an enlarging, aggresive corticotroph pituitary adenoma that can occur following bilateral adrenalectomy performed in the treatment of CD.
The aim of this work is the evaluation of the early and long-term results of the microsurgery in a single surgeon's series of patients with NS
During the period from January 2000 to December 2005 - ten patients with NS have been operated on. The authors analyzed surgical outcome in the NS group of 7 women and 3 men with the mean age of 47.99 years (range 39–66, S.D. ± 8.47 years). NS was diagnosed on the clinical signs and symptoms, especially hiperpigmentation of the skin, elevated serum ACTH level and progression of the pituitary tumor. Parasellar extension of the adenomas was measured according Knosp's scale and Hardy–Wilson's scale in both groups. Pituitary function and radiological examinations were evaluated in the early postoperative time, 30 days after operation and in the follow-up. Histological examination was based on the WHO (2004) criteria.
According to the criteria of the remission of the Nelson's syndrome, 5 patients (50%) were cured.
No perioperative mortality was reported. The three patients presented pituitary insufficiency and two patients - diabetes insipidus. There were no cerebrospinal fluid leakage after surgery. The pituitary carcinoma was recognized in one case. Transsphenoidal microsurgical removal of pituitary adenomas is safe and effective treatment of Nelson' syndrome.

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P943

The impact of the Cushing's Disease remission in associated comorbidities

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Background
The Cushing's disease (CD) is associated with comorbidities that have a significant impact on patients' quality of life. However, it is not known the true impact of the disease remission on these comorbidities.
Objectives
To assess the evolution of comorbidities associated with CD, after its remission.
Methods
It was done an observational, analytical and retrospective study of patients with CD in remission, followed in our department. Clinical data concerning the time of diagnosis (active disease) and 1 year after surgery/radiotherapy (remission) were collected.
Results
Of the eighteen included patients, 77.8% were female and the age at diagnosis was 39.6 ± 15.1 years. Seventeen patients (94.4%) were in remission after surgery and one (5.6%) required adjuvant radiotherapy.
At diagnosis, 12 patients had hypertension, three had type 2 diabetes (T2DM), six dyslipidemia and seven were on psychotropic drugs. After 1 year of remission, there was a significant reversal of hypertension (66.7 *vs* 22.2%, $P=0.008$). There was a decrease, although not significant, in the number of patients on psychotropic drugs (38.9 *vs* 16.7%, $P=0.219$). It was not observed differences in T2DM and dyslipidemia. Eleven patients (61.1%) underwent initial dual-energy X-ray absorptiometry, two had osteoporosis and four osteopenia. At revaluation, patients with osteoporosis normalized *T* score, and in patients with osteopenia one had recovered.
The CD remission was associated with a significant decrease in the patients' weight (75.4 ± 13.3 *vs* 67.3 ± 10.2 kg, $P<0.001$) and BMI (29.0 ± 4.7 *vs* 25.8 ± 3.3 kg/m^2, $P=0.001$). In this analysis, it was excluded a pediatric patient (31.3 *vs* 29.1 kg/m^2). Despite that, four patients (22.2%) remained obese and six (33.3%) overweight.
Conclusion
After 1 year of CD remission, there were significant improvements in hypertension and obesity/overweight. Other comorbidities had also improved, although without statistical significance. Thus, it is crucial to highlight the requirement of maintain surveillance and reassessment of these long-term changes.

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P944

Weight and metabolic profile evolution in patients with treated prolatinomas

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Introduction
The metabolic consequences of hyperprolactinemia and the repercussions of its treatment with dopaminergic agonists are not yet fully understood. This study aims to evaluate the metabolic profile of patients with prolactinomas (prevalence of diabetes mellitus, dyslipidaemia and obesity) and identify the potential variations after treatment with bromocriptine.
Methods
Retrospective study of patients followed between 1962 and 2013. Included 177 cases, 134♀/43♂, with 37.2 ± 13.7 years, 54.8% ($n=97$) macroprolactinomas. Analysed: anthropometric data; treatment; prolactin levels, fasting glucose (FG) and lipid profile. Exclusion criteria: follow-up ≤2 years or introduction of antidiabetic and/or lipid-lowering drugs. Statistical analysis: SPSS (21).
Results
Initial evaluation: BMI: 28.1 ± 4.7 kg/m^2 (obesity in 29.4%); FG: 89.8 ± 24.4 mg/dl (diabetes in 4.5% ($n=8$), 50% ($n=4$) previously documented, and, IFG in 7.3% ($n=13$)); 41.2% ($n=73$) of the patients presented alteration of at least one lipid fraction. Median initial prolactin was 224 ng/dl. Median cumulative dose of bromocriptine administered, during 9.1 ± 7.4 years, was 9672.5 mg. After treatment 83.1% ($n=147$) patients achieved normal prolactin levels. Almost half, 49.2% ($n=87$), of the treated patients presented weight reduction, with significant reduction of final BMI ($P<0.05$). Prolactin normalization constituted an independent predictive factor of weight reduction (OR = 2.97, IC95%: 1.017–7.564: $P<0.05$). There was a reduction in FG in 18.1% ($n=32$) patients, and of those initially with IFG, 46% ($n=6$) presented normal FG after treatment. Weigh reduction sextupled the odds of reducing FG (OR: 6.33, $P=0.012$). About one third of patients improved at least one lipid fraction, with significant reductions of LDL-cholesterol (132.7 *vs* 115.3 mg/dl, $P<0.01$) and triglycerides (139.9 *vs* 110.4 mg/dl, $P<0.01$); and increased HDL-cholesterol (49.2 *vs* 55.5 mg/dl, $P<0.01$). Triglycerides reduction was correlated with weight reduction ($r=0.285$, $P<0.05$).
Conclusion
It was observed a high prevalence of obesity and dyslipidaemia in patients with prolactinomas and a proven benefit of hyperprolactinemia treatment. Treated patients presented weight reduction and improvement of global metabolic profile. The normalization of prolactin levels almost tripled the odds of patients lose weight, which was associated with an improvement of virtually all the evaluated parameters.

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P945

Cushing's disease caused by atypical pituitary adenoma

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Introduction
Cushing's Disease results of corticotrophin (ACTH) hypersecretion from pituitary which increases cortisol production. WHO classified pituitary tumors as typical adenoma, atypical adenoma and carcinoma. Diagnostic criteria for an atypical adenoma include invasive growth, elevated mitotic index, Ki-67 labeling index greater than 3% and extensive p53 immunoreactivity.
Case Report
Sixty-eight years-old man presented to our consult with history of visual complaints, brain MRI showing a 15 mm invasive pituitary macroadenoma and with hormonal testing revealing ACTH 100 pg/ml (9–52), urinary free cortisol (UFC) 591 μg/24 h (10–136) and hypogonadotropic hypogonadism. He repeated UFC that was positive and made a low dose dexamethasone test (LDDST) with no suppression. The results of the high dose dexamethasone test and the CRH test were not suggestive of CD. Inferior petrosal sinus sampling for ACTH was performed only on the right side with no central/peripheral gradient. Neck, chest and abdomen CT showed no significant alterations. He was submitted to transsphenoidal resection due invasive macroadenoma with compressive symptoms, including left ptosis worsening. Tumor pathology showed epithelial neoplasia type with atypia and frequent mitoses. There was diffuse ACTH staining and almost diffuse p53 expression. Ki67 labelling index was 25%. After surgery ACTH 73.6 (<63.3 pg/ml) and LDDST suppression. The patient began treatment with ketoconazole and was proposed for radiotherapy.
Conclusions
Dynamic noninvasive tests were not suggestive of CD, however these tests have poor negative predictive value. Carcinoma is defined by the presence of metastases, who this patient did not reveal. This clinic case illustrates an example of a pituitary tumor with a pathological and immunohistochemical studies indicating a highly proliferative activity, aggressive growth and malignant potential, even so it is classified as atypical tumor. These tumors must have a tight follow-up for early detection of recurrence and/or metastasis.

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Steroid metabolism and action

P946

Measurement of testosterone, androstenedione and dehydroepiandrosterone (DHEA) serum levels using isotope-dilution liquid-chromatography tandem mass spectrometry (ID-LC-MS/MS)

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The adrenal and gonadal androgens testosterone, androstenedione and dehydroepiandrosterone (DHEA) play an important role in sexual development and fertility as well as in several other processes. We developed a method to assess serum testosterone, androstenedione and DHEA levels in one run using isotope-dilution liquid-chromatography tandem mass spectrometry (ID-LC-MS/MS). Sample preparation consisted of addition of internal standards ($^{13}C_3$-testosterone, $^{13}C_3$-androstenedione and $^{2}H_6$-DHEA) and a liquid–liquid extraction using hexane-ether. The samples were analyzed on an Acquity 2D UPLC system (Waters), equipped with a C4 column (Waters) and a Kinetex Fluorophenyl column (Phenomenex), and a Xevo TQ-S tandem mass spectrometer (Waters). The three analytes were baseline separated in a total run time of 9 min.
The intra-assay CVs were <4, <4.6 and <6.2% for testosterone, androstenedione and DHEA respectively. The inter-assay CVs were <7% for testosterone and androstenedione and <9.3% for DHEA. At the lower concentrations inter-assay CVs were 9, 7 and 9.3%, for testosterone (0.08 nM), androstenedione (0.48 nM) and DHEA (1.18 nM) respectively. Recoveries of spiked analytes were 101–107% and 97–106% for testosterone and androstenedione respectively. Recovery of DHEA is under investigation. Linearity was shown in dilution series (mean R^2 was >0.999 for all analytes). This method tested negative for interference from several steroids. The method was shown to be suitable for serum as well as EDTA and heparin plasma.
The present testosterone method compared well ($y = 1.000x + 0.035$ nmol/l; $r = 0.9982$) to another ID-LC-MS/MS method for testosterone in our lab. The latter method being concordant with a published reference method (Bui *et al.* 2013). In the near future, the present method will also be compared to another LC-MS/MS method for androstenedione and DHEA.
In conclusion, we developed a sensitive and accurate method to measure serum testosterone, androstenedione and DHEA serum levels in one run.

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P947

Vitamin D is associated with androgen synthesis in human testicular cells

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Introduction
Testosterone production in male testicular cells is mainly stimulated by LH, secreted by the pituitary. Recent findings have shown significant clinical associations of vitamin D seasonal rhythms and androgens in men (Wehr et al. 2010, Nimptsch et al. 2012). We aimed to elucidate associations of vitamin D and androgen synthesis on a cellular level.
Methods
Human primary testicular cells, isolated from testes of braindead donors, and a cell line of human testis embryonal carcinoma cells (NT2/d1) were cultured in parallel and supplemented with or without luteinizing hormone (LH) in the presence or absence of 1,25-dihydroxyvitamin D (1,25OH2D). Testosterone concentrations in the culture media were measured by ELISA. Gene expression of vitamin D and androgen related genes was observed on mRNA level by RT-qPCR at baseline and after addition of physiological and supraphysiological concentrations of the hormones.
Results
At baseline, vitamin D metabolizing enzymes were expressed in both primary testicular and NT2/d1 cells. Addition of physiological doses of 1,25OH2D increased significantly mRNA levels of both androgenic genes (*HSD3B1*, *CYP11A1*, *CYP19A1*) and vitamin D metabolizing enzymes (CYP2R1, CYP27A1, CYP27B1) in human testicular cells, but not in NT2/d1 cells, where only vitamin D related genes were increased. Supraphysiological doses showed expression patterns similar to physiological doses, however the vitamin D catalysing enzyme CYP24A1 was significantly increased. 1,25OH2D enhanced testosterone synthesis in healthy testicular cells, but not in testicular carcinoma cells.
Conclusion
We demonstrate a significant and reproducible involvement of vitamin D in androgen synthesis in healthy testicular cells. Considering vitamin D as an important player in male androgen synthesis might help defining clinical approaches and a better therapeutic management of male hypogonadism.

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P948

Changes in serum steroid concentrations in relation to fat distribution and insulin resistance in women with polycystic ovarian syndrome

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Background
Polycystic ovarian syndrome (PCOS) affects 5–10% of women of reproductive age. Hyperandrogenism and hyperinsulinaemia have been attributed to the pathophysiology of PCOS. The aim of this study is to evaluate the effect of fat distribution and insulin resistance on steroid metabolism in PCOS.

Methods
The study recruited 20 PCOS and 20 matched controls. Fat distribution was assessed by waist circumference, skin fold measurements, and body mass index (BMI). All underwent an oral glucose tolerance test (OGTT). Blood samples were collected at baseline, 15, 30, 60, 90 and 120 min. Insulin and glucose were measured using Siemens Centaur and Advia-2400 Glucometer. Serum steroids were measured using liquid-chromatography tandem mass-spectrometry (LC-MS/MS).
Results
Baseline measurements showed higher corticosterone ($P=0.04$), 17-hydroxy-pregenelone (17DP) ($P=0.03$) and cortisol ($P=0.03$) in PCOS *vs* control group. Following OGTT, insulin ($P=0.05$) and 17DP ($P=0.06$) showed relatively higher responses (area under the curve) in the PCOS *vs* control group. Fat distribution positively correlated with insulin resistance in PCOS and control groups ($P<0.0001$). The overweight/obese women in both groups were more insulin resistant (higher insulin and HOMA-IR) (both $P<0.001$), had higher baseline dehydroepiandrosterone sulphate (DHEAS) ($P=0.001$) with relatively higher cortisol response ($P=0.06$) after OGTT. Women with high insulinaemia had relatively higher baseline DHEAS ($P=0.05$) and 17DP response ($P=0.06$) after OGTT.
Conclusion
Fat distribution and insulin resistance alter the ovarian and adrenal steroid metabolism in both normal and PCOS women. Metabolism of steroids such as 17DP, corticosterone and cortisol can be altered due to either hyperinsulinaemia or fat distribution showing interplay between both factors

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P949

The role of steroid hormones in the development of postpartum depression

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Introduction
Postpartum depression affects 10–15% women after childbirth. There is no currently generally accepted theory about the causes and mechanisms of postpartum mental disorders. The principal hypothesis concerns the association with sudden changes in the production of hormones affecting the nervous system of the mother and, on the other hand, with the ability of receptor systems to adapt to these changes.
Methods
We observed changes in steroidogenesis in the period around spontaneous childbirth. We performed three samples of maternal blood. The first sampling was 4 weeks prior to term; the second sampling was after the onset of uterine contractions (the beginning of spontaneous labour); the third sampling was during the third stage of labour (immediately after childbirth). Additionally, we collected mixed umbilical cord blood. The almost complete steroid metabolome was analysed by gas chromatography – mass spectrometry followed by RIA for some steroids. Mental changes in women in the peripartum period were observed using the Hamilton Depression Rating Scale. The local ethics committee approved the study.
Results
We found already the changes in androgens levels correlating with postpartum mood disorders 4 weeks prior to childbirth. The strongest correlations between steroid and postpartum mood change were found in samples of venous blood samples collected from mothers after childbirth and from umbilical cord blood. The main role played testosterone, possibly of maternal origin and estrogens originating from the fetal compartment.
Conclusion
These results suggest that changes in both maternal and fetal steroidogenesis are involved in the development of mental changes in the postpartum period. Descriptions of changes in steroidogenesis in relation to postpartum depression could help clarify the causes of this disease, and changes in some steroid hormones are a promising marker of mental changes in the postpartum period.

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P950

Tissue cortisol vs lipolysis in ICU patients

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Introduction
The interplay of cortisol (F) and adipose tissue is complex and in many aspects is still obscure. Plasma F has been shown to be positively associated with lipolysis.
Aim
To study in adipose tissue indices of lipolysis *vs* tissue F with microdialysis (MD).
Subjects and methods
We studied 46 mechanically ventilated patients with a diagnosis of septic/non-septic shock, systemic inflammatory response syndrome or severe sepsis. Upon ICU admission a MD catheter was inserted under sterile conditions into the subcutaneous adipose tissue of the upper thigh. Excluding patients on steroid therapy, on day 2 ($n=26$), day 3 ($n=24$) and day 4 ($n=22$) MD samples were collected six times per day for MD glycerol (MD GLYC; used as an index of lipolysis) and tissue F. The mean of these six collections was used for analysis (normal values for adipose tissue GLYC <200 μmol/l). Statistics were done with Spearman's rank correlation.
Results
Most samplings (44/72) indicated accentuated lipolysis with above-normal MD GLYC levels. MD GLYC was weakly correlated to MD F ($r=0.246$, $P=0.038$).
Discussion
We verified the well-known association (though modestly so) between lipolysis and F (and in particular with interstitial/tissue levels of it). Changes in interstitial/tissue F may not be reflected in plasma (total) F concentrations. Thus it is interesting that we observed an – albeit weak – association between tissue lipolysis (*via* MD GLYC levels) and MD F.

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P951

Testosterone stimulates glucose uptake in HepG2 liver cells

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Introduction
Testosterone deficiency is associated with an increased risk of type-2 diabetes (T2D) in men. Physiological testosterone replacement (TRT) improves insulin resistance and glycaemic control in hypogonadal men with T2D. The mechanisms underlying these actions remain unknown, but may be due in part to an effect on the liver as a major metabolic organ involved in glucose regulation. We have previously shown in testicular feminised mice, which have low testosterone levels and a non-functional androgen receptor, that hepatic expression of glucose regulatory targets (Hexokinase 4, HK4; Phosphofructokinase, PFK; Mitogen-activated protein kinase kinase, MAP2K) were significantly reduced and that TRT increased HK4 expression. Here we investigate the effects of testosterone on glucose uptake and metabolism in human liver cells.
Methods
Glucose uptake was assessed using 2-NBDG, a fluorescent glucose analogue, in HepG2 cells treated with either testosterone (1–100 nM) or vehicle control for 24 h. Cells were analysed for mRNA and protein expression of targets of glucose regulation; HK4, PFK and liver X receptor (LXR), by qPCR and western blotting following 24 h treatment with testosterone or control.
Results
Glucose uptake was increased in testosterone treated cells at 10 nM ($122\pm5.5\%$ of control, $P<0.05$) and 100 nM ($121\pm6.4\%$, $P<0.05$) concentrations compared to vehicle control. HK4 protein expression was increased in 10nM testosterone treated cells vs vehicle control (0.56 ± 0.04 vs 0.24 ± 0.11 arbitrary densitometry units (ADU). $P=0.08$), and significantly at 100 nM concentrations (0.68 ± 0.25 vs 0.24 ± 0.11 ADU. $P<0.05$). No difference was observed between treated and untreated cells for PFK and LXR protein expression and mRNA expression for all targets.

Conclusion
Testosterone increases glucose uptake in HepG2 cells as a mechanism to potentially improve hepatic glucose control and T2D in men. This action may be *via* increased hepatic glycolysis through the upregulation of HK4 expression, a key regulatory enzyme in glycolysis.

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P952

A hypercoagulable state associated with intravenous pulse methylprednisolone (MP) therapy in patients with Graves' orbitopathy

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Introduction
Chronic exposure to glucocorticoid excess, either endogenous or exogenous, is associated with a hypercoagulable state and a high thromboembolism risk. The underlying mechanism of this phenomenon is still unclear. Clinical studies have indicated various abnormalities of procoagulant, anti-coagulant and fibrynolytic factors, e.g.: alterations of clotting factors (F), plasminogen activator inhibitor (PAI-1), plasminogen, antithrombin. Moreover, other consequences of glucocorticoid excess (obesity, insulin resistance, hypertension, dyslipidemia) can cause vascular and endothelial damage which can independently activate coagulation. However, the risk of a hypercoagulable state during intravenous pulse glucocorticoid therapy remains unknown.
Description of methods/design
The aim of the study was to examine the influence of intravenous methylprednisolone (MP) given once a week for 12 weeks (cumulative dose 4.5 g) in patients with active, moderate to severe Graves' orbitopathy (GO) on hemostasis. Parameters examined before and after treatment included: FII, FV, FVII, D-dimer, platelets, APTT, PT. Twenty consecutive patients with GO were included into the study (mean age: 52 years), comprising 14 women and 6 men. All patients were euthyroid during the study. There were no history of venous thromboembolism events, 6 patients had well-controlled hypertension and 1 patient impaired glucose tolerance, 11 patients were smokers. No patients were taking medications that affect hemostasis.
Results
Statistically significant increase of FII ($P=0.001325$), FV ($P=0.031824$), FVII ($P=0.027858$) and platelets ($P=0.042131$) was observed respectively in 90, 75, 70 and 63% of patients. There was observed increase of D-dimer in 55% of patients, and decrease of PT and APTT in 65 and 50% of patients respectively. There were no episodes of clinically overt venous thromboembolism.
Conclusion
High dose intravenous pulse methylprednisolone (MP) in patients with GO may be associated with a hypercoagulable state. In patients with additional risk, prophylactic treatment may be required.

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P953

Adrenal androgen secreting tumour in 39-year-old woman: Hormones and sexuality

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Introduction
Androgen secreting adrenal tumours are rare and sometimes malignant. We report hormonal and sexual changes in 39-year-old woman with androgen secreting adrenal tumour completely healed by resection of the tumour.
Case report
Androgen secreting adrenal tumour that manifested in 39-year-old woman with suddenly appeared amenorrhea, weight gain, hirsutism, epileptic seizures and elevated DHEA-S and testosterone is described. Right adrenal 6–10 cm tumour was detected by ultrasound and confirmed by computed tomography. DHEA-S was three times higher and testosterone was nine times higher than highest normal values. Complete surgical removal of androgen secreting adrenal adenoma conditioned decrease of DHEA-S, testosterone and other adrenal hormones in 2 and 24 h after the surgery. 1 month later all the hormones returned to normal levels. Menses reappeared spontaneously in 6 weeks after a short period of hot flashes and perspirations. Seizures did not appear in 8 months after the surgery. Sexual activity was investigated using FSFI total score (FSFI-TS). Woman was at sexual dysfunction risk (The FSFI-TS $<=26.55$). One month before and 1 month after surgery the FSFI-TS was respectively 19.0 and 25.0. The best sexual function was detected 6 months after the operation (FSFI-TS was 30.1). Desire, arousal and orgasm were better 6 months after the operation comparing before the manifestation of the disease, 1 month before and 1 month after the operation (6.0 vs 4.8 vs 3.0 vs 4.2; 5.7 vs 4.8 vs 2.4 vs 3.9; 6.0 vs 4.4 vs 3.6 vs 4.4).
Conclusions
Appearance of an unusual symptom – seizures and their disappearance after successful removal of the adrenal tumour are highly suggestive about the DHEA-S – induced seizures. This case raises a hypothesis, that controversial changes of sexuality are conditioned by desensitization of testosterone receptors because of constant and long-lasting increase of testosterone secretion.

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P954

Estradiol and its metabolite 2-methoxyestradiol modulate the growth of HECa10 line acting predominantly in the opposite way

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Introduction
The HECa10 line was derived from the specialized endothelial cells typically occurring in lymphoid tissues and belonging to high endothelial vessels (HEVs). Recent studies have shown that HEVs are also present within the tumor microenvironment, what unlike to other blood vessels, can be associated with favorable prognosis of cancer patients. Estradiol (E2) and its metabolite 2-methoxyestradiol (2ME2) are known as the important modulators of cardiovascular system changing growth processes of different endothelial lines. However, there is no data concerning their effect on HEV lines. Thus, we studied the direct effects of E2 and 2ME2 on the growth of HECa10 line *in vitro*.
Methods
The growth of HECa10 line was assessed by two methods: the colorimetric Mosmann's method reflecting total metabolic activity of cultured cells and the fluorescence CyQUANT® method reflecting number of cultured cells. The effect of various concentrations of E2 (mainly physiological) and 2ME2 was examined in 12, 24, 36 and 72 h cultures.
Results
Estradiol in 72 h culture stimulated the growth of HECa10 line with moderate potency increasing number of cultured cells at four concentrations (10^{-7}, 3×10^{-8}, 10^{-8}, 10^{-9} M) and its metabolic activity only at two concentrations (3×10^{-8}, 4×10^{-9} M). However, at another two concentrations (10^{-7}, 4×10^{-9} M) it inhibited metabolic activity of this line. The stimulatory effect of E2 at concentration 10^{-8} M was noted since 36 h cultured.
In turn, 2ME2 inhibited the growth of HECa10 line in 72 h culture with great potency at two the highest pharmacological concentrations (10^{-4}, 10^{-6} M) and with moderate strength at one the lowest tested concentration (10^{-12} M) (physiological concentration) (assessed by two methods). Its inhibitory effect was observed also in 24 and 36 h cultures.
Conclusions
Estradiol and its metabolite 2-methoxyestradiol modulate the growth of HECa10 line acting with different strength and generally in the opposite way.

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P955

Testosterone supplementation and sexual function: a meta-analysis study

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Introduction
The role of testosterone supplementation (TS) as a possible treatment for male sexual dysfunction remains questionable. The aim of the present study is to meta-analyse data evaluating the effects of TS on male sexual function and its therapeutic synergism with the use of phosphodiesterase type 5 (PDE5i).
Methods
An extensive Medline Embase and Cochrane search was performed including the following words: 'testosterone', 'erectile dysfunction'. All randomized controlled trials (RCTs) comparing the effect of TS vs placebo on sexual function or the effect of TS as add on to PDE5ì s on sexual function were included. Data extraction was performed independently by two of the authors (A.M.I, G.C), and conflicts resolved by the third investigator (M.M).
Results.
Out of 1702 retrieved articles, 41 were included in the study. In particular, 29 compared TS vs placebo, whereas 12 trials evaluated the effect of TS as add on to PDE5ìs. TS is able to significantly ameliorate erections and to improve other aspects of male sexual response in hypogonadal patients. However, the presence of publication bias was detected. After applying Duval and Tweedie 'trim and fill' method, the positive effect of TS on erectile function and libido components retained significance only in RCTs partially or completed supported from pharmaceutical companies (CI (0.04–0.53) and (0.12;0.52) respectively). In addition, we also report that TS could be associated with an improvement in PDE5i outcome. These results were not confirmed when placebo-controlled studies were selectively analysed. The majority of them, however, included mixed eugonadal/hypogonadal subjects.
Conclusions
TS plays positive effects on male sexual function in hypogonadal subjects. The apparent difference between industry-supported and independent studies could depend on trial design more than on publication bias. New RCTs exploring the effect of TS in selected cases of PDE5i failure who persistently retain low T levels are advisable.

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P956

Profiling of neuroactive steroids, their precursors and metabolites in patients suffering from multiple sclerosis

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Some steroids modulate the permeability of ionotropic receptors on cell membranes and therefore may activate or inhibit neuronal activity depending on the steroid structure. These neuroactive steroids (NAS) exert neuroprotective effects like the neuronal remyelination.
Multiple sclerosis (MS) is the most common cause of neurological disability in young adults. Therefore, the authors have followed the neuroprotective, GABAergic, glycinergic, glutamatergic acetylcholinergic and purinergic NAS, their precursors and metabolites and their conjugates (64 steroids)in the Δ^4 and Δ^5 steroidogenic pathways, estrogens, 5α/β-reduced pregnanes and androstanes (both 17-oxo and 17β-hydroxy), 7α/β- and 16α-hydroxyderivatives of the Δ^5 steroids, and 20α-hydroxyderivatives of the Δ^4 and Δ^5 steroids, and 5α/β-reduced pregnanes in the circulation and cerebrospinal fluid of 13 female patients – 36 years old median age and 8 sex age matched healthy controls (both in the follicular menstrual phase) with the use of gas chromatography – mass spectrometry. The steroid conjugates were hydrolyzed and the released steroids were detected like the case of the unconjugated ones. The primary finding was the increased levels of C21 steroids in body fluids, which points to increased activity of adrenal cortex as mechanism enabling a consequent synthesis of neuroprotective steroids in various human peripheral tissues. The neuroprotective effects of individual steroids and a possible utilization of the results for the diagnosis and treatment of MS were discussed.

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P957

Role of clinical risk factors and polymorphisms in glucocorticoid receptor gene in the determining the risk of developing new-onset diabetes after kidney transplantation

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Introduction
New onset diabetes after transplantation (NODAT) is a recognized metabolic complication of kidney transplantation: its rates at 12 months after transplantation is between 20 and 50% for kidney recipients and it is associated with increased risks of graft rejection, infection, cardiovascular disease and death. Transplant-specific risk factors for NODAT,such as corticosteroids and calcineurin inhibitors, play a dominant role in its pathogenesis. Furthermore polymorphisms in GR gene are common in the human population and play a role in regulation of glucocrticoid sensitivity.
Objective
Determine the incidence genetic and clinical risk factors for NODAT among kidney recipients in our centre.
Patients and methods
We studied 96 kidney allograft recipients without preexisting diabetes. The presence of arterial hypertension, blood chemistry and BMI were assessed at 3, 6 and 12 months. *GR* gene polymorphism (BclI, A3669G) were analyzed using RT-PCR System and Taqman allelic discrimination assays.
Results
Three months after renal transplantation 27% recipients developed NODAT. There were no significant differences in age, mean daily steroids doses and genetic polymorphism in GR between patients with NODAT and healthy control. Patients with NODAT had a BMI significantly increased compared with healthy control (25.4 vs 21.8, $P=0.02$).
Conclusions
The prevalence of NODAT in our center is similar to that found in the literature. BMI and obesity are a risk factors for NODAT. Age, daily steroids doses and genetic polymorphism in GR are not correlates with its development.

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Thyroid (non-cancer)

P958

A case of primary hypothyroidism: Lingual thyroid

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Lingual thyroid is an abnormal formation appearing as the result of a deficient descent during embryological development of the thyroid gland through the thyroglossal duct to its normal pretracheal location, and it is a rare embryological aberration. A 19 years old woman was admitted to with foreign-body-feeling, dysphonia, hoarseness, constipation. Examination showed a spherical, red fleshy and smooth contoured mass rat back of the tongue. Thyroid scan with technetium 99 m revealed isotope uptake in the base of tongue area and no uptake in the normal thyroid location. With these findings lingual thyroid was diagnosed. Surgical exision was not recommended since the lingual mass was the only functioning thyroid gland and medical treatment was appropriate. We aimed to present a case of lingual thyroid and hypothyroidism with laboratory and imaging findings.

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P959

Urinary iodine excretion in Egyptian females with nodular goiter

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Introduction
Iodine is needed for the production of thyroid hormone. The prediction of iodine intake is difficult. The standard measure of iodine nutrition in a community is the median urinary iodine excretion, expressed in micrograms per liter. According to the WHO, a median urinary iodine excretion of 100–199 µg/l indicates that the iodine intake is adequate.
The aim of this work is to measure the iodine excretion in patients with thyroid nodules in comparison to normal control subjects.
Subjects and methods
Eighty subjects were chosen with thyroid disorder. Sixty female patients: Group I (20 patients with single nodule), Group II (40 patients with multinodular goiter) IIa 28 patients with hypothyroid, group IIb (12 patients euthyroid) Compared to Group III (20 healthy control).
History taking, clinical examination, thyroid ultrasound, thyroid function test, urinary iodine excretion done to all participants.
Results
Urinary iodine excretion in patients with multinodular and single nodule is significantly lowered than in control subjects The mean value of urinary iodine excretion in group I is 22.6 ± 4.7, in group IIa is 22.9 ± 5.9, in group IIb is 30.6 ± 2.8 compared to control group III is 19.2 ± 7.3 with statistical significance ($P < 0.001$).
Conclusion
In our study, an iodine deficiency was observed in all studied patients with thyroid nodule-s whether euthyroid or hypothyroidism. From these results we concluded that reduced urinary iodine excretion in patients is an index of iodine status. Therefore, iodine deficiency contributes to development of thyroid in Egyptian females.

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P960

The FRAX score in postmenopausal women with subclinical hyperthyroidism

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Introduction
FRAX score is the ten-year estimated risk calculation tool for bone fracture which includes clinical data and hip bone mineral density measured by x-ray densitometry (DXA). The aim of the study was to elucidate the ability of the FRAX score in discriminating between bone fracture positive and negative postmenopausal women with subclinical hyperthyroidism.
Material and methods
FRAX score calculation were performed in 27 postmenopausal women with newly discovered subclinical hyperthyroidism (58.85 ± 7.83 age, BMI 27.89 ± 3.46 kg/m^2, menopause onset in 46.88 ± 10.21 years) and 51 matched euthyroid controls (59.69 ± 5.72 age, BMI 27.68 ± 4.66 kg/m^2, menopause onset in 48.53 ± 4.58 years).
Results
In group with subclinical hyperthyroidism main FRAX score was statistically significant higher (6.50 ± 1.58 vs 4.35 ± 1.56, $P = 0.015$). FRAX for hip was also higher in evaluated group than in control (1.33 ± 3.92 vs 0.50 ± 0.46, $P = 0.022$). There was no correlations between low TSH and fracture risk ($P > 0.05$). The ability of the FRAX score in discriminating between bone fracture positive and negative postmenopausal female subjects ($P < 0.001$) is presented by area under the curve (AUC) plotted *via* ROC analysis. The determined FRAX score cut-off value by this analysis is 6%, with estimated sensitivity and specificity of 95 and 75.9%, respectively (Table 1).
Conclusion
Postmenopausal women with subclinical hyperthyroidism have higher FRAX scores and a thus greater risk for low-trauma hip fracture than euthyroid postmenopausal women. Our results point to the need of monitoring peri-menopausal women with subclinical hyperthyroidism for avoidance of fractures.

Table 1 ROC analysis for TSH and FRAX score in group with subclinical hyperthyroidism.

	Area	SE	*P*	95% CI for SE
TSH	0.644	0.162	0.336	0.326–0.961
Main FRAX	0.998	0.003	*0.001*	0.992–1.005
Hip FRAX	0.750	0.192	0.094	0.373–1.127

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P961

Graves' disease presented with renal infarction

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Introduction
There are few cases about arterial thrombosis combined with thyrotoxicosis independent of atrial arrhythmias. Herein, we report a case of Graves' disease presented with renal artery infarction withiout atrial fibrillation.
Case
A 54-year-old man visited the emergency department due to the sudden onset of left flank pain for 30 min. The left flank pain was accompanied by sole dysuria without other symptoms of pyelonephritis. Physical examination showed neck enlargement and eyeball protrusion. He did not have any medical history of diabetes, hypertension, or cardiovascular disease. Vital signs were as follows:blood pressure- 140/90 mmHg, heart rate-108 bpm, respiration rate-22/min, body temperature- 36.5°C. The electrocardiogram (ECG) showed normal sinus rhythm and tachycardia, and chest X-ray was unremarkable. Laboratory findings were as follows: urinary analysis-5–9 RBC/HPF, +1 proteinuria. TSH-0.01 uU/ml (0.55–4.78), freeT_4— 28.33 pmol/l (11.5–22.7), anti-TSH receptor antibody (TSI)-40.00 IU/l (~1.75). Other results were within normal range. Abdominal CT with enhancement showed hypoechoic lesion with clear margin of wedge shape on the left kidney and there was thrombus in left renal artery. Renal artery infarction was diagnosed based on his symptoms and typical CT finding. The patient was treated with intravenous unfractionated heparin infusion. Holter monitoring and echocardiogram showed normal findings. Thyroid ultrasonography showed increased size and vascularity of both thyroid gland. Technetium-99m thyroid scan was also compatible to the Graves' disease. The patient was treated with methimazole and switched to warfarin therapy after 5 days of heparin infusion.
Conclusion
Although the clear relationship between arterial thrombosis, especially renal artery infarction, and hyperthyroidism needs to be clarified in the future, our case suggests that uncontrolled thyrotoxicosis can be associated with a risk of renal artery infarction.

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P962

Female cardiothyrosis

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Introduction
Cardiothyreosis is a severe and most frequent heart complication due to hyperthyroidism. It includes severe arrhythmias, heart insufficiency or heart coronary insufficiency ± atrial ventricular block, or pulmonary hypertension.

Our aim was to study cardiothyreosis frequency in females, its incidence, its causes, and its response to radical treatment.
Subjects and methods
It is a retro-and prospective study which analyzed 1641 female hyperthyroidisms observed over a long period of time (1981–2011).
All patients had clinical examination, routine and hormonal analyses, and heart exploration based on chest X-rays, electrocardiography and echocardiography ± heart MRI and scintigraphy to look for heart complications.
Results
We observed 235 cardiothyreosis (14.32%), 7.8 cases/year, median age = 59.49, the maximum was observed between 1992 and 1996 after iodine supplementation (1990). 68% complicated multinodular goiters vs 28% for auto immune hyperthyroidisms. Auricular fibrillation was observed in 76.52%, heart insufficiency in 50.43%, auricular ventricular block in 1.73% and pulmonary hypertension in 13.4%. Coronary insufficiency was noted in 10.24%. An antecedent of heart disease was found in 60%. Systemic high blood pressure was observed in 19% and diabetes mellitus in 7%. After radical treatment heart complications resolved in 53%.
Conclusion
Cardiothyreosis is frequent in women (14.3%). The most frequent cause was multinodular goiter. The main heart complication was represented by arrhythmias ± heart insufficiency. Coronary insufficiency was observed in 10%. Severe heart complications were observed mainly in women having an antecedent of heart disease. After radical treatment heart complications disappeared in 53%.

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P963

Male cardiothyrosis

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Cardiothyreosis (CT) is defined as an association of hyperthyroidism (HT) with severe heart complications such as rhythmic troubles, heart and/or coronary insufficiency. Recently ventricle-auricular block and arterial pulmonary hypertension (APHT) was added to the definition. CT is the most frequent and one of the most dangerous complications of hyperthyroidism (HT) in emerging countries compared to developed countries where this abnormality is deemed to be very rare. Our aim was to study its frequency, analyze its profile and response to radical treatment in 63 men with cardiothyreosis.
Subjects and methods
It is a retro- and prospective study (1981–2011) which took into account medical history, clinical examination, routine analyses, hormonal and heart explorations based on echosonography, electro radiography ± heart MRI and heart scintigraphy.
Results
Among 447 male HT, 63 had CT = 14%. We observed 3.1cases/year. Mean age at diagnosis = 50.76 years (26–83). 7 (12%) were ≤30 years old. 90% were diagnosed because of rhythmic troubles. A history of heart disease was noted in 70%. Auricular fibrillation was found in 100%, heart insufficiency in 36%, APHT in 12%, and dilated cardiomyopathy in 36%. Glucose metabolism abnormalities were associated in 18%. After radical treatment (surgery or radio iodine) heart problems disappeared in 80%.
Conclusion
CT is very frequent in our population (14%). It is observed in middle age or old people, especially those with an antecedent of heart problems. Radical treatment leads to a good prognosis except when there is a dilated cardiomyopathy. The best treatment is prevention of rheumatic diseases and precocious diagnosis of HT.

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P964

Abstract withdrawn.

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P965

Quality of life is impaired in patients with euthyroid nodular goiter

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Description
Quality of life (QoL) is impaired in patients with thyroid dysfunction but has never been evaluated in patients with euthyroid nodular goiter (ENG). The aim of this study was to evaluate QoL in patients with ENG and compare the results with a healthy control group.
Methods
Thirty patients with ENG (mean age 38.0 years, male/female = 3/27) and 30 healthy, age and gender-matched euthyroid subjects without thyroid nodule (mean age 38.9 years, male/female = 4/26) were included in the study. The groups were questioned and compared with regard to Beck Anxiety Scale (BAS) and Beck Depression Scale (BDS) scores. QoL is evaluated with Short Form-36 (SF-36) questionnaire.
Results
There were no significant differences with regard to age, gender, marital and education status, BAS and BDS scores between the two groups ($P > 0.05$). Mental health and vitality scores of SF-36 were significantly lower in the patient group (P's 0.013 and 0.036 respectively). Physical componet, mental component, physical functioning, role physical, role emotional, social functioning, bodily pain and general health scores were similar between the groups (all P's > 0.05). Physical functioning, bodily pain, vitality and physical component scores of SF-36 were negatively correlated with both BAS and BDS. No correlations were found between SF-36 scores and age, disease duration, thyroid volume and TSH.
Conclusion
QoL (especially sub-scales of mental components of SF-36) is impaired in patients with ENG even though they have no thyroid dysfunction. This impairment is related to anxiety and depression rather than disease characteristics.

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P966

Thyrotoxic periodic paralysis as the first manifestation of hyperthyroidism

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Introduction
Thyrotoxic periodic paralysis (TPP) is a complication of hyperthyroidism characterized by muscle paralysis and hypokalemia. It mainly affects male patients of Asian descent. Many patients do not have obvious symptoms and signs of hyperthyroidism, which makes its diagnosis difficult.
Case report
A 47-year-old Asian man presented with all four limbs rapidly progressive muscular weakness that caused him inability to walk. He referred a previous episode with spontaneous recovery. Guillain–Barre syndrome and spinal cord disorders had been ruled out. He denied fever and any medication in previous days. The physical examination revealed lower limbs proximal weakness (strength 3/5) and areflexia. Blood tests showed hypokalemia, hypophosphatemia, hypomagnesemia, elevated creatine kinase level with normal acid-base balance, decreased TSH level (0.01 μUI/l) and elevated free T4 (2.41 ng/dl). The patient was positive to antimicrosomal and anti TSH-receptor antibodies and negative to antithyroglobulin antibodies. Ultrasonography revealed a heterogeneous and hypervascular thyroid with goitre. The patient was diagnosed with TPP and treated with intravenous potassium supplementation. Full recovery was achieved in less than 24 h. Further treatment with beta blockers and antithyroid drugs was prescribed. Definitive treatment for Graves-Basedow disease with Iodine-131 was scheduled.

Conclusions
TPP is a well-known complication in Asian populations. It is becoming increasingly common in other areas like Europe due to population mobility. The majority of cases are due to Graves' disease although the 90% of patients have clinically silent hyperthyroidism at the time of TPP diagnosis. Thus, thyroid function should be evaluated in patients presenting with muscle weakness and hypokalemia to distinguish it from other forms of hypokalemic periodic paralysis. It is recommended to test thyroid hormones in Asian descent patients presenting with muscle weakness.

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P967

Usefulness of color-flow doppler ultrasonography in the differential diagnosis of thyrotoxicosis in outpatients

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Objective
To evaluate the role of thyroid blod flow assessment by color-flow Doppler ultrasonography in the differential diagnosis of thyrotoxicosis in an outpatient endocrinology clinic.
Material and methods
Consecutive patients with thyrotoxicosis presenting to our center between January–December 2013 were included in the study. Clinical date were collected and measurements of TSH, serum free thyroxine and TSH receptor antibodies were performed. Thyroid glands were evaluated by the same endocrinologist expert in thyroid ultrasound, whith color-flow Doppler ultrasonography (Logic Scan 64, B-Side Medical System) whit a 10-MHz linear transducer. Were assessed size, vascularity and peak systolic velocity of the inferior thyroid artery (PSV-ITA). Gland vascularity was categorized into 4 grades. PSV-ITA >40 cm/s is considered significantly increased, suggestive of Graves' Disease (GD). ^{99m}Tc pertechnetate scan was done in patients when the diagnostic was not clear. *U*-Mann–Whitney test and Fisher exact test were used for statistical analysis.
Results
A total of 45 patients with thyrotoxicosis were enrolled in this study. The suspected diagnostic in the first consultation was: 2 toxic adenomas, 4 toxic multinodular goiters, 24 GD, 15 destructive thyrotoxicosis (DT) (3 type II amiodarone thyroiditis, 3 subacute thyroiditis, 2 Hashitoxicosis, 3 silent thyroiditis) and 4 normal ultrasound. Toxic multinodular goiters and toxic adenomas were confirmed by ^{99m}Tc scan. Intraparenchymal vascularity of thyroid gland was greater in patients with GD than in patients with DT (type 3/4: 100% vs 9% respectively; $P<0.001$). Thyroid blood flow assessed by PSV-ITA was significantly higher in patients with GD than in patients with DT (62.3 ± 13.7 cm/s vs 27.4 ± 9.2 cm/s; $P>0.001$).
Conclusions
The usefulness of color-flow doppler ultrasonography of the thryroid gland goes beyond the assessment of thyroid nodule. In patients with thyrotoxicosis provide valuable information about underlying thyroid functional status and is useful in the differential diagnosis.

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P968

Evaluation of epicardial adipose tissue thickness in patients with overt hyperthyroidism

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Objective
Thyroid diseases are among the most common endocrine disease and with a prevalence of 1.2%. Thyroid hormones have several effects on cardiovascular system. Many studies showed the association between hyperthyroidism and acute ischemic heart disease with conflicting results. Epicardial adipose tissue (EAT) thickness is a marker of atherosclerosis and independent predictor of coronary artery disease. In this study, we aimed to evaluate the EAT thickness in patients with overt hyperthyroidism (OH).
Materials and methods
Thirty newly diagnosed untreated OH patients and 44 control subjects were included in the this study. EAT thickness and carotid intima media thickness (CIMT) were measured by echocardiography.
Results
EAT thickness and CIMT were higher (4.31 ± 1.12 mm, 3.11 ± 0.84 mm, $P<0.001$; 0.62 ± 0.17 mm, 0.50 ± 0.11 mm, $P<0.01$ respectively) in OH patients than in healthy subjects.
Conclusion
In conclusion, EAT thickness was higher in OH patients, therefore EAT thickness together with CIMT may be used as markers of early atherosclerosis in OH patients which had higher cardiovascular mortality than normal population.

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P969

Evolution of thyroid function in Hashimoto's thyroiditis and related disorders–January 2014

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Aim
Analyzing the evolution of thyroid function in thyroiditis and related disease between 1–20 years.
Material and method
i). Diagnostic: Hashimoto thyroiditis (HT): *1*. antithyroperoxydase antibodies (ATPO), cut-off 34 ui/ml. *2*. if ATPO = normal, thyroiditis was considered if high antithyroglobuline antibodies (T-ATG); *3*. idiopathic mixedema (IM): hypothyroidism with no ATPO, no ATG, no TRAB. ***ii).*** Thyroid function: normal TSH: 0.4–4 u/ml. ***iii)***. Statistic analysis: *z* test.
Results
I. HT*:** Re-evaluated patients = 484. ***i). At the diagnostic moment. Euthyroid (EUT): 202 (41.75%), Hypothyroid (HOT): 208 (42.98%), Hyperthyroid (HIT): 74 (15.29%) – all with high TRAB (Graves-Basedow disease-GBD).
ii). Follow-up. *a*. 35 (17.33%) with EUT became HOT after 0.2(!)-8 years (av = 2.88, S.D. = 2.31). *b*. 4 (1.98%) with EUT become HIT (all GBD). *c*. Almost all HOT remained HOT, 1 become HIT (GBD) and still under methimazole. *d*. 41 (55.41) with HIT become EUT after 1.5–2 years and maintain at least 8 years. *e*. 3 (4.05%) with HIT become spontaneously HOT, under levothyroxine, vi). 2 relapsed after 2 years treatment, g. 28 are still under antithyroidian treatment (5 between 5-11 y).
***II. T-ATG*:** Re-evaluates patients = 30. ***A*.** At the diagnostic moment. EUT: 15 (50%, significantly more than in HT), HOT: 12 (40%), HIT: 3 (10%) - only one high TRAB (GBD association).
***B*.** Follow-up. a. 1 EUT (6.67%) become HOT (*vs* HT $P=0.008$). b. 2 HIT become EUT, 1 under treatment. c. All HOT remained HOT.
III. IM
IM: HOT: 86 (100%). All remained HOT after 5–20 years.
Conclusions
i). Thyroiditis with only hyperATG could be considered different from HT: more EUT than HOT, less HOT evolution. **ii).** Only few EUT-HT adult patients developed HOT (17.3%). **iii).** No EUT-HT patient modified function after 8 years of observation. **iv).** Patients with HOT at diagnostic time, either HT, T-ATG or IM, remained HOT.

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P970

Immune associations in chronic thyroiditis – January 2014

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Material and method
i). Patients: A. 'Classical' Hashimoto thyroiditis (hyper-ATPO-emia, HT) = 1293, B. thyroiditis with isolated hyper-ATG-emia, with normal ATPO (T-ATG) = 92, C. thyroiditis 'sero-negative' (normal ATPO and ATG, pathology diagnosis) = 11, D. idiopathic myxedema (hypothyroidism, no A,B,C) = 86; E. control = 1219. **2. Statistical analysis**: X^2 test, z test.
Results
Total Immune Associations (excluding Graves Basedow Disease): HT = 244 (18.87%, $P \ll 0.001$); T-ATG = 23 (25%, $P \ll 0.001$); dif HTvTATG: NS, z = −1.4; 'sero-negative' = 1 (9.09%, NS); idiopathic myxedema = 12 (13.95%, NS); control: 109 (8.94%). 2. Main IA (accordingly to the number): A. Graves-Basedow disease: TH: 161 (12.45%), T-TAG: 5 (5.43%), dif HTvT-ATG: important $P \ll 0{,}001$. B. Drug allergy: HT: 27, $P < 0.008$, T-ATG = 4, $P = 0{,}08$. C. Vitiligo: HT = 37, $P \ll 0{,}001$; T-ATG = only 2. D. Dermatitis: HT = 37, $P \ll 0{,}001$; T-ATG = 4 (NS). E. Immune ovaritis with precocious menopause: HT = 17, $P = 0{,}006$. F. Allergic Rhinitis: HT = 13, $P = 0{,}006$. G. Biermer anemia: HT = 12; $P = 0{,}01$. H. Asthma: HT = 9, NS (control = 10). I. Rheumatoid arthritis: HT = 8, NS (control = 19). J. Repetitive zona zoster: HT = 7, $P = 0.04$; K. Thrombophilia: HT = 7, $P = 0.04$. 3. Multiple associations: HT = 70 (28.7% from HT IA); T-ATG = 5 (21.74% from T-ATG IA). 4. In IA thyroid function and sex was the same as in other patients (in all z test, P = NS).
Conclusions
i). HT and T-ATG has immune associations with increased frequency. **ii).** The most significant and prevalent association are: Graves-Basedow, drug allergy, vitiligo, dermatitis, early menopause with immune ovaritis, allergic rhinitis, Biermer anaemia. **iii).** HT, T-ATG and idiopathic myxedema are not significantly associated with other immune conditions: rheumatoid arthritis, IDDM, B/C hepatitis. **iv).** Multiple immune associations are common.

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P971

Relationships between antithyroperoxydase antibody and antithyroglobulin antibody levels with thyroid function in chronic thyroiditis – January 2014

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Aim and Objectives
Is Hashimoto thyroiditis (HT) different from thyroiditis with only antithyroglobulin antibodies (T-ATG)?
Material and method
i). Diagnosis: ATPO > 34 ui/ml = HT; ATPO normal with high ATG (> 34 ui/ml) = T-ATG. **ii). Thyroid function**: TSH. **iii). Patients:** HT = 1293, T-ATG = 92. **iv). Statistical analysis:** Student tα, linear correlation tests.
Results
A. HT: I. *ATPO*: Average = 691.38. **II.** *Linear correlation ATPO-TSH*: $r = 0.11$, $P < 0{,}001$. **III.** *ATPO by function*: 1. Euthyroidism (EUT) = 575 patients (44.47%), average = 586.33, hypothyroidism (HOT) = 542 (41.92%), average = 846.11, hyperthyroidism (HIT) = 176 (13.61%), average = 558.09, lower than EUT. 2. Statistical differences: ATPO-EUT *vs* ATPO-HOT: $P \ll 0.001$, ATPO-EUT *vs* ATPO-HIT: $P = 0.7$. **IV.** ATG: Average: 465.42. **V.** *Linear correlation ATG-TSH*: $r = 0.096$, $P < 0.01$. **VI.** *ATG by function*: 1. EUT average = 364.98, HOT average = 599.16, HIT average = 325, lower than EUT. 2. Statistical differences: ATG-EUT *vs* ATG-HOT: $P \ll 0{,}001$, ATG-EUT *vs* ATG-HIT: $P = 0.7$.
B. T-ATG: I. *ATPO:* Average = 11.09; S.D. = 8,49. **II.** *T-ATG:* Average = 446.2. **III.** *Linear correlation ATG-TSH*: $r = -0.12$; No correlation. **IV.** *ATG by function*: 1. EUT = 55 patients (59.78%, more than in HT, $z = -2.7$, $P = 0.006$), average = 442.67, HOT = 24 (26.09%, less than in HT, $P \ll 0.001$), average = 314.27, *lower* that EUT, HIT = 13 (14.13%, same as HT), average = 729.412, higher than EUT. 2. No statistical differences ($P > 0.05$) ATG-EUT *vs* ATG-HOT, ATG-EUT *vs* ATG-HIT.
Conclusions
i). Significant correlation exists between thyroid function and both ATPO and ATG *in HT*: in hypothyroid patients, ATPO/ATG were higher than in hyperthyroid and euthyroid patients. ***ii).*** HT *vs* T-ATG evolve with more hypothyroidism *vs* Euthyroidism. ***iii).*** ATG in T-ATG had no relationship with thyroid function. ***iv).*** Thyroiditis with only ATG is a different thyroiditis comparing with Hashimoto thyroiditis.

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P972

Efficacy of different models for explaining the endocrine surgery operative procedure

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The acceptance of any operative or interventional procedures depends on the capability of the surgeon to explain the procedure in detail and also associated complications without undue fear to the patient. The aim of this prospective randomised study is to establish an ideal model for the surgeon to explain. We used three models for explaining the procedure of hemithyroidectomy (removal of diseased lobe plus the isthumus and a cuff of contralateral lobe and pyramidal lobe if present) for benign nodules using conventional diagram model, toy model and using animation model. Each group had 40 patients each after randomisation. Females predominated.The operative procedure was performed by a single endocrine surgeon using sutureless technique and no drain was inserted. Post operatively all patients discharged on the morning after surgery. The toy group and animation group had better idea of the procedure which was rated using an questionnaire. The explanation of the procedure was given by the same surgeon a week before the opeartion in the outpatient department. In the post operative period the animation group had no questions when compared to the other groups($P < 0.05$). To conclude the animation model if available shall be the ideal model for explaining the operative procedure.

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P973

Hyperprolactinaemia in patients with hypothyroidism

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Aim
To determine the prevalence of hyperprolactinaemia in patients with newly diagnosed subclinical and overt hypothyroidism, and to investigate the change in PRL levels during and after the treatment.
Methods
In this study were enrolled 100 patients, which have been diagnosed with hypothyroidism during a 2 year period, in 'IKEDA' hospital, DC 'Med.al' and DC 'La vita', and 100 healthy persons as controls. Lactating and pregnant women, patients with medical reasons for having elevated PRL levels, and persons with kidney and or liver disease were excluded from the study. Serum levels of thyrotropin (TSH), free thyroxine, free triiodothyronine and prolactin (PRL) were measured and correlation of PRL levels with the severity of hypothyroidism (overt or subclinical) was performed.
Results
Thirty-three patients (27 women, 6 men, mean age 42.7 ± 14.1 years) had overt hypothyroidism. Sixty-seven patients (58 women, 9 men, mean age 40.2 ± 12.3 years) had subclinical hypothyroidism. One hundred healthy persons (88 women, 12 men, mean age 41.8 ± 10.5 years) participated as controls. The same blood tests were repeated in patients after normalization of TSH levels with L-thyroxine treatment. The PRL levels resulted elevated in 31% of patients with overt hypothyroidism, and in 20% of patients with subclinical hypothyroidism. PRL levels decreased to normal in all patients after thyroid functions normalized with L-thyroxine treatment. In the hypothyroid patients (overt and subclinical) a positive correlation was found between TSH and PRL levels ($r = 0.203$, $P = 0.001$).
Conclusion
PRL levels are altered in both overt and subclinical hypothyroidism, but they normalize after normalization of TSH, with appropriate L-thyroxine treatment.
Keywords
Prolactin, overt hypothyroidism, subclinical hypothyroidism, hyperprolactinaemia

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P974

Management of hypothyroidism in pregnancy

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Until 12th week of gestation foetus is entirely dependent on maternal thyroxine. Inadequate thyroxine replacement may lead to lower IQ of offspring and also an increased miscarriage rate.
We audited 68 hypothyroid pregnant females to assess whether management of their thyroid status had met current standards. In the first trimester TSH is not an optimal monitoring marker as it is supressed by rising HCG level. According to established clinical guidelines FT4 should be maintained in the upper limit of normal and TSH less than 2.5 mIU/l in the first trimester by appropriately adjusting the dose of levothyroxine.
Sixty-eight hypothyroid pregnant patients presenting in 2012 to Mid-Yorkshire Trust, UK, were identified using the Euroking database and hospital records. Only 49% (33/68 patients) had the thyroid function tests checked by 8th week of gestation to allow sufficient time for adjustment of levothyroxine dosage if required. 18/33 patients required no dose adjustment, 9/33 patients had the dose of thyroxine appropriately increased, 6/33 patients should have had thyroxine dose increased but no adjustment had been made. Of 23/68 patients first tested after 12 weeks gestation, 10 should have had thyroxine increased suggesting the foetus had been put at risk during first trimester.
Only 40% (27/68 patients) actually met the standards of monitoring and dose adjustment, if required, in a timely manner. In order to improve care in line with established clinical standards education of patients and GP practises need to be improved by circulating audit results to GPs and making hypothyroid female patients aware of the need to have their thyroid function tests checked as soon as they become pregnant. We are planning to re-audit in 1 year time to see if compliance with guidelines has been improved.

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P975

Pregnancy outcomes in women with subclinical hypothyroidism

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Aim
To evaluate pregnancy outcomes, such as spontaneous abortion, preterm delivery, and antepartum or postpartum hemorrhage, in relation to thyroid peroxidase antibody (TPOAb) level during thyroxine replacement for subclinical hypothyroidism.
Materials and methods
This study included 50 pregnant women with subclinical hypothyroidism, which were followed from the beginning to the end of their pregnancy. Levothyroxine was supplemented to maintain TSH between 0.3–3 mIU/l in all patients, irrespective of TPOAb status. Pregnancy outcomes were noted as spontaneous abortion, preterm delivery, and antepartum or postpartum hemorrhage. Outcomes were compared between these three groups as per TPO antibody status (undetermined, negative, positive), which were matched for age and gestational period.
Results
In our study, thyroid autoimmunity was noted in 42% of women screened for TPO antibody. A total of 13 adverse pregnancy outcomes were observed (five spontaneous abortions, five preterm deliveries, three postpartum hemorrhage) with no significant difference between the groups.
Conclusion
Adverse pregnancy outcomes resulted similar in the three groups of pregnant women with adequate thyroxine replacement for subclinical hypothyroidism. TSH values maintaining in euthyroid range, irrespective of thyroid autoimmunity status, is an important factor for pregnancy complicantions prevention.
Keywords
Pregnancy, subclinical hypothyroidism, preterm delivery, spontaneous abortion, thyroid autoimmunity.

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P976

Serum C-reactive protein level is a better indicator than erythrocyte sedimentation rate in assessing the severity of inflammation before initiation of glucocorticoid therapy in the sub acute thyroiditis patients

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Background
Serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are useful indicators of inflammation in patients with sub-acute thyroiditis. Despite the widespread use of several diagnostic tests, the purpose of this study was to compare the usefulness serum CRP and ESR in deciding which patient requires of glucocorticoid therapy.
Methods
A total of 28 patients with sub-acute thyroiditis, included in this study. Serum CRP and ESR measured in all the patients. The characteristics of these tests were assessed with use of two different techniques: first, receiver-operating-characteristic curve analysis was performed to determine the optimal positivity criterion for the diagnostic test, and, second, previously accepted criteria for establishing positivity of the tests were used.
Results
Fifteen out of 28 patients were found to have features of significant thyroid inflammation eventually requiring glucocorticoid based on current recommendations. The receiver-operating-characteristic curves indicated that the optimal positivity criterion was 19.3 mg/l for the C-reactive protein level and 46 mm at 1st h for the erythrocyte sedimentation rate. C-reactive protein level with sensitivity of 0.67, specificity of 0.92, positive likelihood ratio of 8.67, and accuracy of 0.64 appeared better than erythrocyte sedimentation rate which showed sensitivity of 0.93, specificity of 0.53, positive likelihood ratio of 2.02, and accuracy of 0.60.
Conclusions
Serum CRP level provided clear advantage over ESR as a diagnostic test with respect to the assessment of inflammation prior to initiation of glucocorticoid therapy in sub-acute thyroiditis. However a well powered study is needed to examine the clinical relevance of such a role for CRP in thyroidology.

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P977

Body mass analysis in patients with Hashimoto thyroiditis

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Aim
In Hashimoto thyroiditis (HT) thyroid cells show abnormalities in the intracellular iodine metabolism, associated with the changes in the expression of key proteins involved in the biosynthesis of: thyroid peroxidase (TPO), thyroglobulin (Tg), sodium iodide symporter (NIS) and pendrin. The aim of the present study was to compare the expression of thyroid-specific genes, such as NIS and Tg, as well as pro-inflammatory cytokines, such as tumor necrosis factor-α (TNFα) and interleukin 1β in patients with HT and healthy individuals.
Subjects and methods
Thyroid cell were obtained from 39 patients with HT and 15 controls by an ultrasound guided fine-needle aspiration biopsy. Gene expression was assessed by quantitative RT-PCR.
Results
The patients with HT had significantly lower Tg and NIS mRNA ($P=0.002$ and $P=0.001$ respectively), as well as higher TNFα mRNA expression ($P=0.049$) than the controls. In the HT group Tg mRNA expression correlated positively with NIS mRNA expression ($R=0.739$, $P=0.0001$) and thyroid volume ($R=0.465$, $P=0.0005$), as well as negatively with TNFα mRNA expression ($R=-0.490$, $P=0.001$) and anti-peroxidase antibodies (TPOAb) level ($R=-0.482$, $P=0.0002$), whereas NIS mRNA expression correlated positively with thyroid volume ($R=0.319$, $P=0.02$), as well as negatively with TNFα mRNA expression ($R=-0.529$, $P=0.0006$), TNFα serum concentration ($R=-0.320$, $P=0.001$) and TPOAb level ($R=-0.422$, $P=0.001$).
Conclusions
Our results suggest a decreased Tg and NIS expression in thyroid cells of the patients with HT, which may result in reduced active iodide transport and thyroid hormone biosynthesis, as well as reduced thyroid volume. We should also

mention that higher TNFα mRNA expression and serum TNFα concentration in the patients with HT, as well as a positive association between TNF-α and TPOAb levels might confirm a contribution of this pro-inflammatory cytokine to the development of Hashimoto thyroiditis.

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P978

Body mass analysis in patients with Hashimoto thyroiditis

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Introduction
Thyroid hormones deficiency in the course of subclinical and overt hypothyroidism is frequently related to the increased body mass, reduced thermogenesis and metabolic rate however the pathogenesis of improper body mass in Hashimoto thyroiditis (HT) patients is still an open question. Therefore, in the present study we compared body mass and body composition between the patients with Hashimoto thyroiditis who were in clinical and hormonal euthyreosis and healthy individuals who had never been treated for autoimmune thyroid disorders.
Material and methods
The group studied consisted of 53 patients with HT in euthyreosis and 28 healthy individuals. All the patients underwent thyroid ultrasonography and body mass analysis with the use of a medical analyzer InBody 200. Blood samples were also analyzed for TSH and anti-thyroid antibodies.
Results
The patients with HT had higher body mass ($P=0.008$), BMI ($P=0.02$), WHR (0.01) and fat mass ($P=0.02$) than had the controls. In HT group increased body mass was observed in 72% of the patients (overweight in 38% and obesity in 35% of them), as compared with 38% of overweight/obesity in the control group. Thyroid volume was significantly lower ($P=0.01$) and anti-peroxidase antibodies level was two times higher in the group with the treatment period >2 years, but the patients with relatively short treatment period were 7 kg heavier and their fat mass was 6 kg higher than in the subjects treated longer than 2 years.
Conclusions
Our results suggest that the patients with HT, even in euthyreosis, have significantly higher body mass, BMI, WHR and fat mass than healthy individuals, which is probably associated with previous disturbances that led to the increase in fat mass at the stage of hypothyroidism. The observed changes tend to normalize during L-thyroxine replacement therapy.

Keywords
Thyroid, thyroiditis, body mass index, thyrotropin
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P979

Ultrasound-guided thyroid fine needle aspiration with rapid on-site evaluation of adequacy: data from the clinic of endocrinology of a Greek tertiary general hospital in 2013

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Introduction
Ultrasound-guided fine needle aspiration biopsy (US-FNAB) enables selective sampling of thyroid follicular cells while minimizing potential complications. Inadequate specimen sampling can lead to FNAB repeat. Our aim was to evaluate the morphological and cytological characteristics of thyroid nodules with US and rapid on-site evaluation of adequacy (ROSE).
Methods
Two independent endocrinologists evaluated nodule characteristics of 171 US-FNAB performed in 2013. Decision of US-FNAB was based on size, rate of growth, echogenicity, microcalcifications, vascularity, irregular margins and max/min diameter. ROSE was performed after alcohol fixation on glass slides and staining with Hemacolor solution.
Results
Adequacy rate was 92.4%. Thyroid nodules were reported as category I (7.6%), II (84.21%), III (0.58%), IV (1.17%), V (2.34%) and VI (4.09%) based on Bethesda criteria. No difference was observed between patients with benign nodules (BN) and those with malignant/suspicious ones (M/S) regarding mean age (54.9 ± 11.66 vs 53 ± 23.26 years), maximum diameter (2.2 ± 0.97 vs 2.24 ± 1.02 cm) or max/min diameter (1.84 ± 0.56 vs 1.63 ± 0.37). BN were 44.4% hypoechoic, 51.4% isoechoic and 4.2% echogenic whereas M/S 57.1%, 35.7% and 7.1% respectively. Microcalcifications were detected in 52.1% of BN and 71.4% of M/S. BN were characterized by no vascularity, peripheral, central and combined vascularity in 30.6%, 38.9%, 9% and 21.5% respectively, whereas M/S in 14.3%, 42.9%, 21.4% and 21.4% respectively. BN were characterized by irregular margins in 25.7% and M/S in 57.1% ($P=0.008$). Max/min diameter <2 was detected in 69.44% of BN and in 78.57% of M/S. A correlation between age and nodule size was reported in the BN ($P=0.008$) and all-patients group ($P=0.003$).
Conclusions
Thyroid ultrasound and US-FNAB provide direct, real time information. ROSE can provide a high adequacy rate, saving time and economical resources while minimizing patient inconvenience.

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P980

An ectopic thyroid tissue presenting as anterior mediastinal mass in a breast cancer patient

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Introduction
Ectopic thyroid tissue is the result of abnormal gland migration from the foramen caecum to its normal pretracheal position. An ectopic thyroid can be lingual (at the base of the tongue), sub-lingual (below the tongue), prelaryngeal (in front of the larynx), or can be found at other rare sites. The most frequent noncervical location for ectopic thyroid tissue is the thoracic cavity. Here we discuss about a rare case of mediastinal ectopic thyroid tissue presenting with a superior mediastinal mass compressing the brachiocephalic truncus without any symptom in a patient with breast cancer.
Case
An 61-year-old nonsmoker female patient with an incidental finding of a mediastinal mass on Thorax CT scan for following up of breast cancer had consultated us from medical oncology department. Her previous medical history included chronic obstructive pulmonary disease, hypertension, type 2 diabetes mellitus. She had two operation for breast cancer and multinodular goiter before.Thyroid stimulating hormone (TSH), free thyroxine (fT4) and the titers of serum thyroid auto-antibodies were within the normal range. She had history of chest radiation and chemotherapy because of breast cancer. Her thyroid was not palpable, and there was no evidence of cervical lymphadenopathy. An ultrasound of the remnant thyroid identified only two solid nodules. A CT scan of the thorax revealed a 4.7×3.0 cm heterogeneously enhanced mass in the superior mediasten. The mass was located at the intersection of the caudal margin of the left brachiocephalic vein and assendan aorta, and it compressed the brachiocephalic truncus. However, there were no symptoms related to the com-pression. Tc-99m pertechnetate thyroid and mediastinal scintigraphy revealed a mass which was 4 cm and increased uptake in superior mediasten (Ectopic thyroid or metastatic lesion?). As it can the mediastinal metastasis of the breast cancer that can uptake technesium, total body scanning with I-131 revealed which showed increase uptake of iodide in the superior mediastinal mass with $4.5\times4.0\times5.5$ cm dimensions. The mass was resected totally. Histopathological examination revealed nodular colloidal goiter.
Conclusion
Ectopic thyroid is a rare condition, and its location in the mediastinum is even rarer. Although entirely intrathoracic ectopic thyroids are rare, they must be considered in the differential diagnosis of all mediastinal masses. Thoracotomy or sternotomy is required for resection of the mass and prognosis is excellent following a successful excision.

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P981

Hyperthyroidism in a pregnant woman who had hypothroidism due to Hashimoto disease before

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Introduction
Pregnant women with known hypothyroidism must have monthly follow up with thyroid function tests. Appropriate L-thyroxin replacement dose can be given due to trimester specific thyroid stimulating hormone (TSH) levels. We will discuss about a hyperthyroid pregnant woman who was taking L-thyroxin replacement before and during the first trimester of pregnancy for hypothyroidism.
Case
A 24-year old woman came to our out-patient clinic for fatigue and weight gain. She had a family history of Hashimoto thyroiditis. Her TSH was 10.13 uIU/ml (0.27–4.2), free T4 was 1.27 ng/dl (0.9–1.7), free T3 2.98 pg/ml (1.8–4.6), anti TPO Ab was 11.8 IU/ml (0–34) and anti thyroglobulin was 17.27 IU/ml (0–115). Her thyroid ultrasonography was compatible with chronic thyroiditis. L-thyroxin replacement was started after Hashimoto disease diagnosis. After euthyroidisim achieved she became pregnant. With monthly follow up L-thyroxine dose adjusted. On the 20th week of pregnancy thyroid function tests revealed thyrotoxicosis. Despite cessation of L-thyroxin treatment thyrotoxicosis persists and when we take the titer of thyrotropin receptor stimulating antibody (TSHR Ab) it was 405 u/l (0–14). There was no ophthalmopathy on physical examination. Propylthiouracil treatment was started. And she had a healthy boy baby with no obvious thyroid dysfunction.
Conclusion
TSHR Ab is responsible for two distinct clinical syndromes. Stimulating antibodies (TSAb) cause thyrotoxicosis when blocking antibodies (TBAb) cause hypothyroidism. Antibody switch can occur during some periods one of which is pregnancy. The etiology of this process remains unknown but hemodilution of TBAb titer can be one of the possible mechanisms. This is at least one of the important issues that close follow up is mandatory during pregnancy.

	TSH	fT4	fT3
Prepregnancy	10.13	1.27	2.98
11th week (while taking l-thyroxin)	3.13	1.46	2.89
20th week (l thyroxin stopped)	0.02	1.89	6.23
26th week (PTU started)	0.006	3.24	12.13

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P982

Treatment of severe thyroid function disorders and observed changes in body composition

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Hyper- and hypothyroidism are accompanied by significant changes in basic metabolic rate, balance of catabolic and anabolic processes, thermogenesis and ultimately in body weight. The aim of this pilot study was to estimate changes in body composition during certain stages of treatment in patients with severe hypo- and hyperthyroidism; current relation between observed hormonal status and body composition and ultimately the relation between changes in body composition and changes in current hormonal values.
The study included 70 consecutive subjects recruited in outpatient clinic with an initial diagnosis of thyroid function disorders (m/f = 22/48, mean age = 46.3 ± 14.8). Body composition analysis and hormonal assessment were performed at the moment of the diagnosis (V1), 3 months after treatment induction (V2) and after normalization of hormonal values (V3). Finally, euthyreosis was restored in 18 subjects with hyperthyroidism (m/f = 4/14, mean age 38.55 ± 12.7) and 27 subjects with hypothyroidism (m/f = 8/19, mean age 46.8 ± 16.46), whose data was further analyzed.
As a result, patients with symptomatic hyperthyroidism, presented a decrease in total body mass with a simultaneous loss in muscle mass and body fat. In a group of individuals with hypothyroidism, weight gain resulted mainly from the increase in fat mass. Additionally, in the first stage of treatment, only body weight and fat content were significantly correlated with an actual hormonal values. However, each change of body composition was strongly associated with the change in patients' hormonal status. It may be the effect of both direct and indirect influence of thyroid status on body metabolism.

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P983

Role of conventional ultrasonography and shear wave elastography in selection lesions for fine needle aspiration biopsy in multinodular goiter - preliminary study

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Introduction
According to a high prevalence and relatively low occurrence of malignancies in thyroid nodular disease (TND), the selection of suspicious lesions for fine – needle aspiration biopsy (FNAB) seem to be a vital problem in the daily endocrinological practice. Beside deciding if the FNAB is necessary, frequently the second problem occurs – which nodule or nodules should be chosen in case of multinodular goiter (MNG), when the number of potential lesions for FNAB is high. The goal of this study was to compare the usefulness of conventional ultrasonography (US) and novel method of tissue stiffness assessment – shear wave elastography (SWE) – in the differentiation between malignant and benign nodules and in the selection of most suspicious lesions in MNG.
Materials and methods
Subjects with MNG, referred for thyroidectomy irrespectively of indications for surgery, underwent thyroid US and SWE before the surgical procedure. Results of these examinations were further correlated with the histopathological outcomes.
Results
Eighty patients with 339 thyroid nodules were included. Ten thyroid cancers (TCs) in ten patients were diagnosed in histopathology. All ten malignancies were the least elastic lesions in MNG (using quantitative data on maximal tissue stiffness). Four cancers appeared the biggest lesions in MNG, while one was equally the biggest in particular goiter (there were other lesions with the same size) taking into account maximal diameter. Three of ten cancers possessed the highest number of suspicious features in MNG, further four had the highest number equally with at least one other lesion in the same goiter.
Conclusions
On the basis of our results the relatively high stiffness of the lesion – in comparison with other nodules from same MNG, should be considered as strong argument for choosing this particular one for FNAB.

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P984

Does iodine status have an impact on thyroid parameters in healthy pregnant women during the first trimester?

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Introduction
Iodine deficiency has serious consequences for both the mother and the offspring, it is a real public health problem. Our aim was to study the iodine status impact on thyroid parameters during the first trimester of pregnancy in women free of any current or previous thyroid disease.
Patients and methods
Prospective study, on 145 pregnant women (mean age of 29.4 ± 0.5 years) at 10.4 ± 0.2 weeks of gestation. Women with disrupted thyroid balance, who smoke (active smoking confessed) and those followed for thyroid disease or taking medications that interfere with the thyroid gland were excluded. Study protocol: clinical examination, TSH, free thyroxine (FT_4), free triiodothyronine (FT_3), thyroid antibodies (peroxidase antibody and thyroglobulin antibody), and cervical ultrasonography. Statistics tests: collection of data on EPI INFO 5.1, bivariate analysis (the χ^2 test, the Pearson χ^2 test, the Yates corrected χ^2 test, the Wilcoxon χ^2 test (Log rank sum) or Mann–Whitney), the variance analysis method (ANOVA), the correlation test, significance level $P < 0.05$.
Results
Expressed as median: urinary iodine was 200.0 µg/l, iodine deficiency (< 150 µg/l) was observed in 31.7%, FT_4 was 14.1 pmol/l, FT_3 was 4.9 pmol/l,

TSH was 1.2 mIU/l, and thyroid volume was 6.2 ml. We did not find any correlation between urinary iodine excretion and FT_4 ($r=0.12$, $P=0.31$), FT_3 ($r=0.19$, $P=0.12$), TSH ($r=0.13$, P 0.29), and thyroid volume ($r=0.10$, $P=0.38$).

Conclusion

About 31.7% of pregnant women, in the first trimester, free of any current or previous thyroid disease had an iodine deficiency. There was no correlation between urinary iodine and thyroid parameters.

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P985

This is why we recommend the screening for hypothyroidism in pregnant women

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Introduction

Hypothyroidism is known for its adverse effects for both the pregnant woman and her offspring. Our aim is to highlight the benefits of screening for hypothyroidism in all pregnant women with and without risk factors.

Patients and methods

Prospective study, on 270 pregnant women. Women with disrupted thyroid balance, who smoke (active smoking confessed) and those followed for thyroid disease or taking medications that interfere with the thyroid gland were excluded. Study protocol: clinical examination, urinary iodine, TSH, free thyroxine (FT_4), free triiodothyronine (FT_3), peroxidase antibody (TPO-ab), thyroglobulin antibody (Tg-ab), and TSH receptor antibody (TSI), and cervical ultrasonography. Statistics tests: collection of data on EPI INFO 5.1.

Results

The mean age of our patients was 29.4 ± 0.4 years, 41.5% were nulliparous, 25.2% primiparous, 33.3% multiparous. Serum TSH level was normal in 77.8% of cases, FT_4 in 88.5%, FT_3 in 96.7%, two patients had a gestational transient hyperthyroidism, hypothyroidism concerned 11.5% of pregnant women (overt form in 3% and sub-clinical one in 8.5%). Of all hypothyroid patients, 35.5% had not any high risk factor for thyroid dysfunction.

Conclusion

In light of our results, screening all pregnant women for hypothyroidism appears necessary even if it is still not recommended by the various scientific societies.

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P986

Polymorphisms within genes encoding co-stimulatory molecules modulate the susceptibility to Graves' disease and orbitopathy

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The clinical presentation of Graves' disease (GD) depends on the combination of environmental and genetic factors. The *CTLA-4* and *CD28, ICOS* genes encoding negative and positive regulator of the T-lymphocyte immune response, are candidate genes for conferring susceptibility to thyroid autoimmunity.

Polymorphisms in genes: CTLA-4: g.319C>T (rs5742909), c.49A>G (rs231775), g.*642AT(8_33), CT60 (g.*6230G>A, rs3087243), Jo31 (g.*10223G>T, rs11571302), CD28: c.17+3T>C (rs3116496) and ICOS: c.1554_4GT(8_15) were determined in 172 GD patients and 381 healthy persons. Data were analyzed in the context of familial history of thyroid disease, response to the anti-thyroid treatment and severity of Graves' orbitopathy (GO).

Carriers of G allele in marker CT60 (genotype GG and/or GA) had increased risk of GD 1.80 ($P=0.04$, OR = 1.80, 95%CI: 1.03–3.14). Carriers of alleles with 12–21 AT repeat at g.*642AT (8_33) were 1.84-more prone to the disease ($P=0.001$, 95%CI: 1.26–2.69). The multivariate logistic regression analysis showed that only g.*642AT (8_33) marker is an independent risk factor for disease ($\chi^2=33.3$, $P=0.0008$). Moreover, CT60G allele and presence of G allele significantly reduced the rate of a successful medical anti-thyroid treatment ($P=0.002$, and $P=0.01$ respectively). Similar results were observed for marker Jo31. The multivariate logistic regression analysis showed that only the CT60 marker is an independent risk factor of the progression of GD ($\chi^2=114.6$, $P=0.009$). We also observed that carriers of *CTLA-4*g.319C>T CC genotype were over-represented in a subgroup with familial history of thyroid disease (81.2% *vs* 47.1%, $P=0.00005$). Carriers of c.49A>G G allele more often develop severe GO ($P=0.02$, OR = 2.17, 95%CI:1.10–4.30). Moreover, patients carrying allele of 12–21 AT repeat at g.*642AT(8_33) more often develop severe GO ($P=0.01$, 95%CI: 1.19–4.53). The multivariate logistic regression analysis pointed that g.*642AT (8_33) marker as well as male gender are independent risk factor for GO ($P=0.04$, and $P=0.00008$ respectively).

Our results suggest that polymorphisms within gene encoding the CTLA-4 molecule influence the risk of GD and modifies the clinical course of the disease.

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P987

Comparison of aspiration vs with-out aspiration fine-needle biopsy of thyroid nodules for adequacy of cellularity according to Bethesda system

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Introduction

Fine-needle aspiration (FNA) is a simple, the most cost-effective, less invasive and a commonly used diagnostic tool for evaluating thyroid nodules. Recent times a tech-nique called fine-needle sampling non-aspiration (FNNA) or fine-needle capillary thyroid biopsies (FNC) has been more preferred. This technique prevents the use of suction so there is no aspiration crush and there-fore nondiagnostic outcomes are reduced. The aim of this prospective study was to compare the FNA and FNNA with reference to diagnostic adequacy and diagnostic to according Bethesda system.

Materials and methods

Ultrasonography-guided FNA and FNNA biopsy were performed successively on 100 nodules. Both the techniques were done at the same nodules and assessed by the same pathologist, beginning with the first (FNA) on half of the patients (randomly selected) and *vice versa*. The pathologist was unaware of the sampling method employed (FNA/FNNA) for any particular set of slides to avoid individual bias. The final cytopathologic finding was reported by using the Bethesda criteria, in which a sample is considered adequate if it contains a minimum of six groups of well observed follicular cells, with at least ten cells per group.

Results

During this study interval, FNA and FNNA were performed on 100 thyroid nodules in 78 women and 21 men (age range, 19–75 years). The sizes of the thyroid nodules biopsied ranged from 6 to 59 mm in mean diameter. A significant difference between FNA and FNNA examination was found on inadequate results (42% *vs* 22%, $P=0.02$). There was no significant difference nodule characteristics included echogenicity, sonographic criteria, calcification and nodule size between the two techniques.

Conclusion

FNNA technique is easier to perform with better patient compliance. Our study adds a further suggestion to prefer FNNA for reduce nondiagnostic results.

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P988

Long-term efficacy of ultrasound-guided laser ablation for solid thyroid nodules. A three-year multicenter prospective randomized trial

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Background

Thermal ablation techniques are reported to significantly decrease thyroid nodule volume in several single-center short-term series. The present trial on ultrasound

(US)-guided laser ablation (LAT) of solid thyroid nodules is addressed to assess long-term clinical efficacy, side-effects and variability of outcomes in different centers operating with the same LAT procedure.
Patients
Two hundred and one consecutive patients were randomly assigned to a single LAT session (Group 1) or follow-up (Group 2) at four thyroid referral centers. Entry criteria were: solid thyroid nodule with volume >5 and <18 ml, repeat benign cytological findings, normal thyroid function, no autoimmunity, no thyroid gland treatment.
Methods
Group 1: LAT was performed in a single session with two optical fibers, a 1.064 nm neodymium yttrium-aluminum garnet laser source, and an output power of 3 watts. Energy delivery was 3,600 joules for nodules up to 13 ml and 7,200 Joules for nodules larger than 13 ml. Volume and local symptoms changes were evaluated 1, 6, 12, 24 and 36 months after LAT. Side effects and tolerability of treatment were registered. Group 2: follow-up with no treatment.
Results
Group 1: Volume decrease after LAT was $-49\pm\%$, $-59\pm\%$, $-60\pm\%$, and $-58\pm\%$ at 6, 12, 24 and 36 months respectively ($P<0.001$ vs baseline). LAT resulted in a nodule reduction $>50\%$ in 67.3% of cases ($P<0.001$). Pressure symptoms decreased from 31 to 5% of cases ($P=0.002$) and cosmetic signs from 74 to 12% of cases. The procedure was well tolerated in most (92%) of cases. One case of vocal cord paresis self-resolved in two weeks. No changes in thyroid function were observed. In Group 2 nodule volume increased at 36 months ($25\pm 42\%$; $P=0$) and local symptoms worsened not significantly.
Discussion
A single LAT treatment of solid thyroid nodules results in a significant volume reduction with improvement of local symptoms and signs. These effects are persistent on the long-term in absence of relevant side-effects or thyroid function changes.

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P989

Radio frequency ablation (RFA) and percutaneous laser ablation (PLA) in the treatment of thyroid nodules under ultrasound (US) guidance: Preliminary evaluation

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Purpose
The purpose of our study is to compare the effectiveness of PLA and RFA procedures in the treatment of benign thyroid nodules discussing indications, techniques, complication and outcomes derived from our experience.
Method and materials
Thirty-eight patients (26F; 55 ± 14) with benign thyroid nodules were treated, 15 with PLA and 23 with RF. Nodules were classified as thy2 through two consecutive fine-needle-aspiration (FNA) and selected for their clinical implications due to their volume. All of them presented a solid component of over 80% of its total volume, assessed by pre-treatment US evaluation. Right after the ablation procedure, treated nodules were evaluated with a contrast-enhanced ultrasonographic (CEUS) examination in order to assess the area of necrosis. Then patients were followed-up at one week with US, at one month with CEUS, at six and 12 months with US in order to assess nodule's volume reduction and treatment outcomes.
Results
Reduction in nodules volume after RFA has been found to range 27–55% at one month follow-up and 57–84% at 12 months; PLA resulted in a nodule's volume reduction of 25–50% at one month and 51–79% range at 12 months. No Significant differences has resulted between the two techniques in terms of nodule's volume reduction. No Procedural complications occurred.
Conclusion
RFA and PLA are excellent and safe procedures in the management of benign thyroid nodules. Safety represents the primary treatment prerogative, hence the clinical presentation and the radiologist skills should play an important role in the procedure planning; our experience suggested that the choice between RFA and PLA could be made on the basis of where the nodule is sited and on its morphologic features, preferring RFA for more superficial and irregular-shaped nodules and PLA for deeper and plongeant ones.

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P990

The prevalence of coexistence thyroid carcinoma and thyroid nodules in hyperthyroid patients of San Juan City Hospital

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Hyperfunctional nodules of the thyroid are rarely associated with thyroid cancer, for these reason are rarely biopsied. Although multiple theories have being proposed, the relationship is still uncertain. After performing a MEDLINE literature search, we found in multiple retrospectives analysis, that patients with hyperthyroidism with hyperfunctional nodules have an estimated of 0.3–16.3% prevalence of malignancy. In our study forty-eight hyperthyroid cases were prospectively investigated to provide information about the association between hyperthyroidism and thyroid cancer. Historical, biochemical and radiological characteristics of the case subjects and their nodules were also analyzed. All nodules greater than 1 cm in diameter, nodules 5–10 mm size diameter if they had calcification were fine-needle biopsied (FNAB) under ultrasound guidance. The biopsy samples were cytologically asses (by the BETHESDA classification) and we found 77% of benign nodules, 2% of nodules presented with atypia of undetermined significance or follicular lesion of undetermined significance, 8.3% were malignant nodules, and 10.4% were nondiagnostic or unsatifactory. All patients with a biopsy diagnosis of malignant underwent surgery. Thyroid malignancy (micro- or macrocarcinoma) diagnosed pre-operatively in all four cases by US-guided FNAB was confirmed by the pathology obtained after the surgery. Papillary thyroid carcinoma was identified in two patients (4.17%), and Follicular thyroid carcinoma was found in two patients (4.17%). These data demonstrate a higher than expected incidental cancer rate in hyperthyroid patients compared with euthyroid subjects with nodular goiter. Our purpose is to stress the point that, although hyperfunctioning thyroid nodules are rarely described as malignant in the literature, FNAB should not be restricted to cold nodules, in view of our data and others published reports.

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P991

Multifocal sclerosing thyroiditis: a case report

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Introduction
Multifocal sclerosing thyroiditis (MST) is a recently proposed histopathological diagnosis for thyroidectomy specimens that have ≥ 1 radial scar-like foci. Despite the inclusion of the term thyroiditis, MST is not related to other well-known types of thyroiditis and does not have a specific clinical presentation.
Case report
A 30-year-old female presented clinic due to thyrotoxicosis. She did not have any symptoms related to thyrotoxicosis. Upon physical examination her thyroid gland was grade 1b diffuse palpable; the remainder of the examination was unremarkable. Her thyroid hormone values were, as follows: sT_3: 6.7 pg/ml (2–4.4 pg/ml); sT_4: 2.4 ng/d/ (0.93–1.7 ng/dl); TSH: 0.06 μIU/l (0.27–4.2 μIU/l). Antithyroid autoantibodies were negative. Thyroid USG was performed in order to determine the etiology of thyrotoxicosis and showed multinodular goiter. A 99m-Tc pertechnetate thyroid scan was performed for functional assessment of solitary thyroid nodules and two cold nodules were noted.
USG-guided fine needle aspiration biopsy of the cold nodules was performed twice. Cytopathological evaluation yielded non-diagnostic findings for both nodules. After improving thyrotoxicosis, total thyroidectomy was performed by a surgeon. The largest diameter of the thyroidectomy specimen was 4.5 cm in the right lobe, 5 cm in the left lobe, and 3 cm in the isthmus. The cut surface showed multiple star-like fibrotic foci, the greatest diameter of which was 0.6 cm between colloidal nodules. Microscopic examination showed entrapping follicular structures with reactive atypia in the periphery of these fibrotic foci. None of the fibrotic foci exhibited neoplastic transformation. Hyperplastic thyroid follicles were observed in the remaining thyroid gland. Based on the histopathological analysis, MST was diagnosed.
Conclusion
Herein we reported a case of MST as a means to increase clinician awareness, as it may be encountered more frequently in the future.

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P992

Virtually-tracked US-guided radio frequency ablation of benign thyroid nodules: preliminary evaluation

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Purpose
Our purpose was to evaluate the safety and effectiveness of a virtual needle tracking system for US-guided percutaneous RFA of benign thyroid nodules (BTN) as compared to standard RFA.
Method and materials
A STARmed (Korea) 18G bipolar RF electrode was used to perform the BTN ablation procedures. A US machine (LOGIQ E9, GE Healthcare) with a low magnetic field generator was used; electromagnetic sensors, calculating their mutual position, were set on the US probe and on the needle bottom (VirtuTRAX, CIVCO); the system shows the expected path of the needle and its tip position. US-guided RFA were made with a in-plane approach on 23 patients (18F; 57±14) with BTN, randomized in two groups: 13 (group A) were treated with RFA using the Virtual Tracker, 10 (group B) without it. A contrast-enhanced US follow-up was performed after one week in order to have a precise assessment of the area of necrosis in each patient.
Results
In all 23 cases a wide area of nodule ablation was safely obtained. The positioning system accurately guided the needle tip inside the target and allowed for a correct treatment of the lesions with RF. A significant increase of the area of necrosis after RFA was found in group A compared to group B ($P<0.01$). No periprocedural complications occured.
Conclusion
The Virtual tracker allows to easily perform nodules RFA with US-guided approach, providing the clear visualization of the virtual needle tip and shaft, even if the real needle is not visible due to the ablation artifact. The excellent level of safety provided by the virtual tracker allows to perform RFA with high confidence achieving a shortening of the learning curve and granting a significant increase in the nodule area of ablation.

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P993

Mean platelet volume in euthyroid patients with Hashimoto's thyroiditis

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Aim
Hashimoto's thyroiditis (HT) is an autoimmune disease in which a breakdown of immune tolerance is caused by interplay of a variety of immunologic, genetic, and environmental factors. Mean platelet volume (MPV) is the measure of platelet size. MPV possibly is a simple way to estimate platelet activity. Activated platelets play an important role in the pathogenesis of vascular disease especially coronary heart diseases. Larger platelets are metabolically and enzymatically more active and have greater protrombotic potential. In this study we aimed to investigate MPV levels in euthyroid Hashimoto's thyroiditis patients.
Materials and methods
Fifty-one euthyroid patients with Hashimoto's thyroiditis attending to our outpatient clinic of endocrinology department and 51 age and body mass index matched healty subjects were included this study. All patients with HT were euthyroid state. Anti-thyroid peroxidase (anti-TPO) antibody and anti-tiroglobulin (Anti-Tg) antibody were positive. All the study subjects were evaluated by biochemical and platelet parameters.
Results
There were no significant differences in age (33.88±12.87 and 30.18±12.43 year respectively $P>0.05$) and BMI(23.55±3.34 and 22.25±3.65 kg/m^2 respectively $P>0.05$) between study and control groups. Anti-TPO and anti-Tg levels were significantly higher in study group (anti-TPO 428.32±668.39 IU/ml in HT group; 14.85±9.66 IU/ml in control group, $P=0.001$; Anti-Tg 320.46±796.05 IU/ml in HT group, 21.28±26.24 IU/ml in control group, $P=0.09$). There were no significant differences in term of serum FT_3 (3.10±0.37; 3.29±0.76 pg/ml), FT_4 (1.22±0.42; 1.46±0.78 pg/ml), and TSH (1.76±0.79; 1.85±1.14 uIU/ml respectively) levels between study and control group. Serum trigliyceride levels were significantly higher in study group than control group (133.81±91.50 and 90.18±41.15 mg/dl respectively $P=0.015$) but serum total cholesterol, fasting glucose, low density lipoprotein and vitamin B12 levels were similiar between two groups. Mean MPV levels was significantly higher in HT group than those control subjects (8.8±1.05 and 7.9±0.79 fl respectively, $P=0.0001$). To assess the correlation with MPV, a Pearson correlation analysis was performed on each variable. There were positive correlations between anti-TPO and MPV level ($r=0.246$, $P=0.042$) and between anti-Tg and MPV level ($r=0.256$, $P=0.033$). The multiple regression analysis of MPV and other risk factors was performed. Age, BMI, CRP and waist circumference were independent predictive factors of MPV. Adjustment for other these factors did not alter these relative risks.

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P994

Frequency of isolated maternal hypothyroxinemia at gestational diabetes mellitus

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Aim
Our aim was to investigate the frequency of isolated maternal hypothyroxinemia (IMH) at gestational diabetes mellitus (GDM)
Material and method
Fifty women with GDM aged between 20–41 and 100 healthy pregnant aged between 17–41 were involved to study. Patients that have thyroid disease and low free T_4 levels at first trimester were ruled out. Thyroid function tests of patients and healthy controls were assessed at first, second and third trimester with standard reference ranges (SRR) and method specific trimester reference ranges (MSTRR).75 gram glucose tolerance test was performed to all participants at 24–28 week.
Findings
In both patient and control groups 1st trimester fT_4 levels ($fT4_1$) were inside normal SRR and there was not any statistical significance. Ft_4 levels that measured at 2nd and 3rd trimester($fT4_2$ and $fT4_3$) were under normal reference ranges in GDM group and GDM group had statistically significant low values. When assessed the $fT4_2$ and $fT4_3$ with MSTRR, GDM patients had lower levels but both $fT4_2$ and $fT4_3$ levels were inside the normal ranges ($P<0.05$).IMH frequency due to SRR in GDM and control group was 56 and 13% respectively at 2nd trimester, 88 and 44% at 3rd trimester. IMH frequency due to MSTRR in GDM group was 12–36% at 2nd and 3rd trimester respectively, in control group there was not any IMH at 2nd trimester and 1% at 3rd trimester.
Conclusion
Overt, subclinical maternal hypothyroidism is associated with significant adverse events to both mother and fetus. But knowledge about IMH is limited. It is not clearly known whether IMH is a physiologic change or a marker of a subclinical thyroid disease. Thyroid hormones have a role in regulation of insulin secretion. The relationship between thyroid hormones and diabetes was revealed in many studies. Furthermore few studies showed that hypothyroidism increases the insulin resistance. Due to increase in IMH frequency in our study, our results suggest that IMH may be associated with insulin resistance as seen in overt and subclinical hypothyroidism.

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P995

Hyperthyroidism one of the cause of pulmonary hypertension

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Introduction
Hyperthyroidism is a common endocrine disorder that is associated with prominent cardiovascular manifestations. Recent studies also suggest a potential link between hyperthyroidism and pulmonary hypertension (PH). Right-sided heart failure with clinical manifestation is only occasionally seen in patients with Graves' disease. The prevalence and pathogenic mechanisms of hyperthyroidism-related PHT remain unclear but based on literary data an autoimmune mechanism associated with vascular endothelial damage appears to have played a key pathogenic role.
Case report
We present a case of 26 years old young woman with a relapse of Graves' disease. She has been treated for hyperthyroidism in 2008 with antithyroid drugs for 2 years. Patient was admitted to our Department with a 1 month history of generalized weakness, palpitations and intolerance of physical activity, physical examination showed a marks of a right-sided heart failure, exophtalmus and diffuse enlargement of thyroid, ECG showed atrial fibrillation 200/irreg. Patient was treated for hyperthyroidism with propylthiouracyl (PTU) for 1 month (TDD 100 mg), treatment was accompanied with adverse effect on hemopoesis, patient had a pancytopenia. Thyroid state showed hyperthyroidism, TSH-receptor antibodies TRAb were 6.2 (RR 0–1 IU/l). Echocardiography showed reduced left ventricular function, moderate tricuspid regurgitation with pulmonary artery systolic pressure 90 mmHg. Tromboembolism as a reason of PH was excluded. Treatment with PTU was stopped and started a treatment with metimazol (TDD 30 mg), loop diuretics and katecholamines. After treatment we have observed improvement of laboratory findings, normalisation of EFLV, PH decreased. We observed regression of right-sided hearth failure. Definitive treatment of hyperthyroidism will be necessary after achievement of euthyroid state.
Conclusion
Graves' disease may be one of the reason of cardiovascular complications, particularly atrial fibrillation, pulmonary hypertension and heart failure.

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P996

Irisin – newly discovered adipo-myokine and its association with thyroid function – preliminary study

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Introduction
Irisin is a recently reported adipo-myokine. To date, many researchers underline its significant influence on the body metabolism and thermogenesis. Secreted by muscle and adipose tissue irisin promotes a program of subcutaneous white adipose tissue 'browning'. As a result, heat production and general energy expenditure raise. Irisin is considered to be a potential mediator of the health-promoting role of physical exercises. Its possible compensatory role in metabolic regulation was also suggested.
Aim
The main goal of the project is to asses serum irisin concentration in patients with thyroid function impairment and its correlation with creatine kinase (CK) level.
Methods
A studied group consisted of 20 patients newly diagnosed with thyroid function impairement at our department. All subjects underwent routine clinical examination, laboratory tests (irisin, thyroid-stimulating hormone – TSH, free thyroxin – FT4 and triiodothyronine – FT3, and CK concentrations), thyroid ultrasound examination. The associations between irisin, TSH, free thyroid hormones, creatine kinase were analyzed statistically. Furthermore, the difference between irisin serum concentration in hypothyroid and hyperthyroid patients was evaluated.
Results
The negative correlation between the irisin and TSH level was demonstrated ($r=-0.4924$, $P=0.023$), as well as positive correlation between the irisin and FT4 level ($r=0.4833$, $P=0.036$). CK level was negatively correlated with irisin, FT4 and FT3 concentrations ($r=-0.7272$, $P=0{,}014$; $r=-0.9636$, $P\leq 0.0001$; $r=-0.8838$, $P=0.0.0007$ respectively). The mean serum irisin level was lower in hypothyroid than hyperthyroid patients, at the border of statistical significance ($P=0.0726$).
Conclusions
Obtained results suggest the influence of thyrometabolic state on irisin concentration; lower irisin level was found in patients with hypothyroidism. This might be explained with muscle destruction, demonstrating with high CK level.

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P997

Thyroid function during pregnancy

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Background
The levels of maternal thyroid hormone concentrations increase from early pregnancy, with a mild increase in free hormones in the first trimester with a corresponding lowering of serum TSH. Thyroid autoantibodies are found in 5–15% of women during childbearing age, and chronic autoimmune thyroiditis is the main cause of hypothyroidism. Thyroid hormone contributes critically to normal fetal brain development. In the first trimester, the 'normal' range is reduced to 0.1–2.5 mIU/l, and in the second and third trimester is 3.0 mIU/l.
Aim
The aim of this study is to analyse concentration of thyroid hormones and the presence of TPOAb.
Material and methods
This study included 77 healthy pregnant women in the first trimester of pregnancy registered in Center for endocrinology CC Kragujevac. Blood samples were collected for fT3, fT4, TSH and TPOAb and measured by RIA method.
Results
We studied 77 healthy pregnant women in the first trimester of pregnancy. The mean age of patients was 30.8 ± 4.7 years. The prevalence of autoimmune thyroid disease was 25.9%, positive family history for thyroid disorder was in 9%, smoking in 23.4% patients. The average serum level in patients without autoimmune thyroid disease ($n=46$) for fT4 was 10.68 ± 2.16 pg/ml, for fT3 was 2.67 ± 0.49 pg/ml, and for TSH was 2.09 ± 1.11 mIU/l, but 37% women had increased TSH level (more than 2.5 mIU/l).
Conclusion
Our study showed that most of women during of first trimester of pregnancy had concentrations of thyroid hormones in reference range.
Keywords
thyroid function, pregancy

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P998

FT3 level is a predictor of mortality in hemodialysis patients in 5 years follow-up

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Introduction
The low FT3 syndrome is known as associated with a high risk of death within a short time. Less is a long-term observations, and only a few concerning patients on chronic dialysis.
The aim of the study was to evaluate whether the value of thyroid hormones on hemodialysis are a predictor of risk of death in the follow-up of 5 years.
Results
The study included 89 patients (58 men) undergoing dialysis in the period from 01 Jan 2008 to 30 Jun 2013. In this time 55 people died, 7 received a kidney transplant, 27 is still on dialysis. The probability survival was significantly

positively correlated with baseline FT3. Patients alive after 5 years had a higher initial level of FT3 (2.74±0.55 pg/ml) than patients died during the 5 year follow-up (2.51±0.56 pg/ml), but the difference was significant in the test Mann–Whitney ($P<0.05$), indicating rather non-homogeneity both groups than the simple proportionality.
In 2008, 47% of patients had FT3 below the normal range at our lab, and in 2013 55% of those who survived 5 years. Such relationship was not found for FT4 or TSH. While it was slow but statistically significant increase in TSH values with time on dialysis ($P<0.05$).
We also found a statistically significant negative correlation between dialysis adequacy ratio kt/v, with the level of FT4, in the both surveys from 2008 and from 2013.
Conclusion
Examination of the pituitary–thyroid can be useful in assessing the risk of death of patients on chronic dialysis and dialysis adequacy.

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P999

Serum leptin levels among women with and without autoimmune thyroid disease in euthyroid state

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Introduction
Autoimmune thyroid disease (AITD) with elevated antithyroid peroxidase antibodies (aTPO) levels appear in 12–25% of women and is observed more frequently in patients with polycystic ovary syndrome and endometriosis. Some data showed the interference of elevated thyroid antibodies and infertility and worsening quality of life.
Aim
The aim of the study was to determine serum leptin levels among AITD(+) and AITD(−) patients.
Material and methods
In the study were involved 74 patients. All women were hospitalized in Department of Gynaecological Endocrinology because of irregular menses or/and hypo/hypermenorrhoea. In all patients hormonal profile was determined by serum levels of: aTPO, TSH, fT4, FSH, LH, estradiol, progesterone and testosterone. Patients were divided into two groups: AITD positive (aTPO+) and AITD negative (aTPO−).
RESULTS
Leptin serum concentration (ng/ml) was significantly higher in AITD(+) compared to AITD(−): 17.13±7.66 to 12.78±7.28 ($P<0.05$). LH level (mIU/ml) was different in analysed groups: 7.13±8.39 in AITD(+), 4.3±3.06 in AITD(−) ($P<0.05$).
There were not found differences in age between both groups: 37.56 years ±7.67 in AITD(+), 34.73 years ±6.14 in AITD(−) ($P=0.1$). BMI was similar in both groups: AITD(+) *vs* AITD(−) was: 22±3.49 *vs* 23.5±4.35 ($P=0,29$). TSH and fT4 did not differ between groups. TSH (uIU/ml) in AITD(+) was 1.467±0.79, in AITD(−) 1.32±0,73 ($P=0.44$); fT4 (pmol/l) in AITD(+) was 13.71±2.56, in AITD(−) was 13.66±1.68 ($P=0.92$).
There were no differences in serum concentration of FSH, estradiol, progesterone and testosterone between both groups.
Conclusions
Leptin and LH serum concentration are higher in patients with autoimmune thyroid disease in euthyroid state than in patients without autoimmune thyroid disease.

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P1000

Delayed puberty and early menopause in women with GH deficiency

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Introduction
Involvement of growth hormone in the maturation and function of the ovary is proved by a series of clinical observations.
Scope
Assessing serum levels of IGF1 as a marker of GH activity correlated to age of onset of menarche and menopause.
Method
The study groups consisted of 41 patients (group 1) with GH deficiency diagnosed before the age of 8 years and a group of 18 adult patients with pituitary dwarfism who had early menopause (group 2).
Results
In group 1, baseline IGF1 was low for 23 patients and normal in basal conditions for 18 patients. After treatment with recombinant GH, the IGF1 value led to 'normal' in 18 patients in group 1. Age of onset of menarche has been 17±2.84 years in group 1 and 15±2.2 years for group 2. For patients with low IGF1 after GH substitution treatment, menarche was installed at age of 19.3±1.16 years. A total of 11 patients were treated with recombinant GH in prepubertal period. IGF1 value was consistently lower in 14 patients, the remaining 4 patients IGF1 values were within normal limits.
Conclusions
IGF1 deficient values are involved in late maturation of ovarian function in its early exhaustion. Dosage IGF1 could be considered as a predictive factor for ovarian disorders in this population. It remains to note that treatment with recombinant GH in adulthood may extend ovarian activity.

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P1001

Amyloid goiter as an unusual presentation of primary systemic amyloidosis: A case report

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Introduction
Deposition of amyloid substance within the thyroid gland causing clinically appearent enlargement of the gland is described as amyloid goiter. Although microscopic deposition of amyloid substance in thyroid gland is common in systemic amyloidosis, occurence of amyloid goiter is rare.
Case
A 55 years old male patient, who had been diagnosed with multinodular goiter for 10 years, was admitted to our clinic with complaint of increased swelling in his neck during the last 3 months. Physical examination revealed grade 3 palpable thyroid gland. Laboratory testing confirmed euthyroid status. On USG of the neck extensive enlargement of thyroid gland and multiple nodules, largest being 35 mm in size, was evident. On neck CT, the thyroid gland was extented into upper mediastinum and narrowing the trachea was evident (Default 1). Bilateral total thyroidectomy was performed and 380 g 15×11×5 cm sized thyroid mass was excised. Histopathological examination revealed deposition of homogenous eosinophylic appearanced amyloid substance in thyroid gland stroma. Immunhistochemical examination was negative for Amyloid A. Biopsy sample of bone marrow revelaed hypocelluler bone marrow with amyloid deposition and the patient was treated with VAD (vincristine, doxorubicin, dexhamethasone) for the diagnosis of primary amyloidoza.
Conclusion
Amyloid goiter as first sign of systemic amyloidozis is very rare condition. Thyroid gland amyloid deposition is more often occurs secondary and rarely to the primary amyloidozis. Presence of goiter have been reported in 0.04% of the cases with primary systemic amyloidozis. In cases with sudden enlargement of thyroid glands, amyloidosis should be considered as another possible cause alongside with malignancies.

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P1002

Thyroid disorders in systemic lupus erythematosus: Influence of hypothyroidism on clinical manifestations and analytical parameters

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Introduction
The association of systemic lupus erythematosus (SLE) and dysthyroidism has been reported by several studies in a wide range of variability but studies focused

on the influence of hypothyroidism on classic manifestations of SLE are scarce. Our purpose was to evaluate the prevalence of thyroid diseases in a cohort of SLE patients and the relevance of hypothyroidism with clinical and analytical parameters related to lupus.
Methods/design
One hundred and three SLE patients underwent clinical examination and laboratory evaluation for thyroid hormones and the presence of antithyroid antibodies. Clinical manifestations and laboratory data of SLE between euthyroid and hypothyroid patients were compared.
Results
Twenty-four (23.3%) SLE patients had thyroid dysfunction. Prevalence of hypothyroidism was 17.5% (44.4% autoimmune in nature), subclinical hyperthyroidism 1.9% and euthyroid sick syndrome 3.9%. Patients with overt hypothyroidism, when compared with subclinical hypothyroidism, were significantly ($P<0.03$) younger and had a longer duration of SLE (35.4 ± 9.5 *vs* 46.5 ± 10.6 years and 14 ± 4.2 *vs* 7.7 ± 3.8 years respectively). Arthritis showed a significantly lower prevalence in patients with hypothyroidism when compared with euthyroid group (10.3 *vs* 30%; $P=0.04$) and its absence was more frequent in those with a longer duration of SLE. No difference in any analytical parameter between euthyroid and hypothyroid group of patients was found.
Conclusion
Hypothyroidism has little influence on classical manifestations of SLE. The lower frequency of arthritis in patients with hypothyroidism should be considered with caution since it was observed in subjects with longer SLE duration and received more number of treatments. Our data suggest that a most active search for thyroid dysfunction must be done in patients with an earlier onset of the disease.

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P1003

Relationship between hypothyroidism and autoimmunity in systemic lupus erythematosus patients: An initial approach

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Introduction
Hypothyroidism is the most frequent thyroid disorder in patients with systemic lupus erythematosus (SLE) but the cause of this association is not well established. Moreover, no studies focused on the possible relationship between some specific immunologic patterns of SLE and the development of hypothyroidism have been reported.
Methods
In our study, we determined the immunological features and the thyroid status of 103 consecutive patients with SLE in a cross-sectional study. Complete immunological profile was done in all patients. Also, laboratory evaluation for free serum triiodothyronine (FT3), free thyroxine (FT4), thyroid stimulating hormone (TSH), antithyroglobulin antibodies and thyroid peroxidase antibodies was performed.
Results
About 94% were females, mean age: 38.2 ± 14.5 years and mean duration of SLE 8.8 ± 6.2 years. Hypothyroidism was found in 17.5% (44.4% autoimmune in nature). No specific pattern of anti-DNA was more prevalent in patients with hypothyroidism. Hypothyroidism was significantly more frequent in patients with simultaneous positivity for autoantibodies Ro60, Ro52 and anti-La/SSB (25% *vs* 9,7%; $P=0.027$). Regardless of thyroid status, patients with more number of positive autoantibodies had higher TSH value but significant difference was not observed. Prevalence of autoimmune nature of hypothyroidism was higher in patients with two or more positive results for SLE-autoantibodies but the small number of patients in our cohort did not allow us to find significant difference (42.9 *vs* 14.3%; $P=0.53$).
Conclusions
Our data suggest that hypothyroidism is frequent in SLE and it could be influenced by immunological features. Therefore, we conclude that ordering thyroid test in SLE patients with more than one positive result for SLE autoantibodies is recommended. However, studies with a larger number of patients are needed to confirm this hypothesis.

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P1004

Thyroid disorders in adults after oncologic treatment in childhood

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Introduction
The length of patient survival after cancer treatment is increasing and, in some cases, does not differ from the average life span in healthy individuals. The aim of the study is to evaluate thyroid function after oncologic treatment in children.
Description of Methods
A group of 158 patients aged 16–25 who underwent oncologic treatment in childhood and the control group – 66 children and young adults were examined. The prospective study was conducted in the period between 4 and 19 years after the diagnosis. After physical examination, the levels of TSH, fT4, and fT3 (Abbott), as well as TPO Ab and Tg Ab (DAKO Denmark) were assayed and TSI Ab (BRAHMS Germany) levels were measured in patients with hyperthyroidism. The ultrasound of the thyroid gland was done using a Siemens-2000 device.
Results
The prevalence of hypothyroidism in the group of patients was statistically significantly higher than in the control group (27.2 *vs* 6.1%. $P=0.001$). The occurrence of primary hypothyroidism was correlated with the total anthracycline dose and with the total X-irradiation (XRT) dose. The incidence of autoimmune thyroid diseases was statistically significantly higher in children after BMT. There was a statistically significantly higher prevalence of thyroid nodules in children after oncologic treatment. The nodules developed more frequently after XRT anticancer therapy and their prevalence was correlated with the total XRT dose.
Conclusions
i) Primary and secondary hypothyroidism is more prevalent in patients who have received oncologic treatment than in healthy individuals.
ii) Cytostatics, especially anthracycline, and XRT have an effect on the development of primary hypothyroidism.
iii) BMT in children has a significant effect of development of hypothyroidism in the course of AITD.
iv) Cytostatic treatment and XRT contribute to development of potentially neoplastic thyroid nodules.

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P1005

Iodine deficiency in Belarus: state of the problem

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Introduction
Belarus is included into an iodine deficiency region of Central Europe. Therefore the National program widely was introduced from 1999. This program included salt iodization with KIO_3, using of iodizated salt in the food industry and in the field of catering.
The purpose of the research is iodine status monitoring in the Republic of Belarus from 1999 to 2012.
The investigations included determination of the thyroid gland volume by ultrasonography and urinary iodine excretion.
Analysis of studies conducted in Belarus on the iodine status assessment showed that simple nontoxic goiter incidence for the period since 1998 fell with 379.9 people per 100.000 population to 31.91 in 2012 in adults. Reduction of the goiter incidence correlated positively with the urinary iodine excretion increasing. Since 2004 urine iodine excretion monitoring showed the sustainable maintenance of targets in random samples of the population. The median urinary iodine excretion rose from 46.9 μg/l in 1999 to 184 μg/l in 2012.
Conclusion
According to the presented results Republic of Belarus belongs to the countries with sufficient iodine intake. Due to the complex of problem solution, adequate iodine consumption in a food is almost reached in Belarus and significantly the thyroid gland diseases prevalence decreased. This results were confirmed in 2013 ICCIDD in published results iodine intake assessment in the world.

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P1006

A case with silent thyroiditis accompanied by repeated deep vein thrombosis

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Case presentation
A 40-year-old woman was admitted to the department of cardiology in our hospital due to iliofemoral deep vein thrombosis (DVT) in August 2010. It seemed that thrombosis was induced by the oral contraceptive (OC) which she had taken. Her serum level of von Willebrand factor was elevated. After the admission, the insertion of a temporary inferior venous cava (IVC) filter and thrombectomy were performed as well as starting of thrombolytic therapy and discontinuing of OC. She was referred to our department for the evaluation of thyrotoxicosis detected from laboratory tests on admission. Silent thyroiditis based on Hashimoto disease was diagnosed from the endocrinological evaluation. After a stent was implanted into left iliac vein, she discharged with anticoagulation therapy. Her thyroid hormone levels decreased under normal range in October 2010 and we started low dose of levothyroxine treatment and thyroid-stimulating hormone (TSH) was controlled within normal range around 1.5 U/ml. In November 2011, TSH level declined to 0.76 U/ml and dose of levothyroxine was reduced. The iliofemoral DVT recurred in December 2011 and apparent hyperthyroidism was observed. This suggests that silent thyroiditis had recurred just before the recurrence of DVT in this case.
Discussion
Specific stimulation of coagulation factor VIII (FVIII) by triiodothyronine is suggested to be a mechanism of thrombosis caused by thyrotoxicosis. It is known that serum level of von Willebrand factor, which elevated in this case, is one of the indicators for activity of FVIII. Previous studies indicated that thrombosis seems to occur in the circumstance existing not only thyrotoxicosis but also other factors that can induce thrombosis including OC taking and intravascular stents. Although we usually suppose that silent thyroiditis improves without any serious problems, this case shows us that it can induce thrombosis especially in patients who have high risk of thrombosis.

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P1007

The metabolic syndrome, and not obesity, is associated with fasting TSH in euthyroid obese children and adolescents

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Increased serum TSH has been reported in obese children and adolescents and is considered an adaptive mechanism secondary to obesity. This study was undertaken to test the hypothesis that this adaptation is not associated with obesity *per se* but with its related metabolic alterations. Using a cross-sectional approach, we collected retrospectively fasting serum TSH concentration (if within the normal range), anthropometric parameters and criteria for the diagnosis of the metabolic syndrome in 697 Italian, euthyroid children and adolescents attending a University Pediatric Outpatient Obesity Clinic. The metabolic syndrome was absent in non-obese overweight subjects, but its prevalence was 7 and 8% in moderately and severely obese individuals. Serum TSH correlated with BMI, systolic blood pressure, the lipid profile and the metabolic syndrome. In a subset of patients in which additional biochemical parameters were available TSH also correlated with insulin, HOMA-IR, HbA1c and the white cell count. The metabolic syndrome and not obesity, was independently associated with the fasting TSH levels in the regression analysis. In conclusion the metabolic syndrome, and not obesity, was independently associated with higher serum TSH concentration in obese children and adolescents with normal thyroid function. Even if TSH at the high limit of the normal range probably reflects a mechanism of adaptation and not a causal factor in these youngsters, it should be tested as a potential marker of metabolic and cardiovascular risk.

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P1008

Recurrence of Graves' disease after radioiodine treatment: factors related to treatment failure

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Introduction
Radioiodine (RAI) therapy is an inexpensive and reliable therapeutic option for Graves' disease (GD). However, individual characteristics of the disease can influence therapeutic success. The identification of these factors may help to predict outcome and select optimal pre-treatment conditions.
Aim
To assess clinical, laboratory and radioactive parameters that may lead to RAI treatment failure in patients with GD**.**
Material and Methods
Retrospective study of 251 consecutive patients with GD treated with RAI therapy between January/2003 and February/2011. From those, 43 patients relapsed and needed additional RAI therapy-cases. Another 43 patients with therapeutic success (defined as euthyroidism/hypothyroidism 36 months after a single course of radioiodine therapy) were randomly selected-controls. The following parameters were analysed: age, gender, previous therapy with anti-thyroid drugs, thyroid function tests, thyroid mass, 24 h radioiodine uptake(24 h-RIU), administered therapeutic activity and time until relapse, using SPSS 21.0®.
Results
Cohort of 251 patients, 202 female and 49 male, mean age 47±15.3 years. Relapse occurred in 43 patients (17.1%) 15.2±11.3 months after therapy. The case-control analysis showed a significantly higher initial FT4 (4.4±1 ng/dl *vs* 2.8±1.2 ng/dl;$P>0.001$) and TRAb (79±78.5 U/l *vs* 13.4±10.5 U/l; $P<0.001$) in the group with relapse. Regarding previous therapy with anti-thyroid drugs, the relapse group was more frequently treated with propylthiouracil compared with the control group (62.8% ($n=27$) *vs* 12% ($n=10$); $P<0.001$). The odds ratio of relapse in the patients treated with propylthiouracil compared with patients treated with methimazole was 6.171 ($P<0.001$). Patients with relapse had significantly higher mean thyroid mass (77.1±35.5 g *vs* 42.9±20.8 g; $P<0.001$) and 24 h-RIU (59.7±11.1% *vs* 55.5±14.1%; $P=0.048$). There were no differences concerning administered therapeutic activity between groups (1414.4±170.2 MBq *vs* 362.6±114.7 MBq; $P=0.952$). The thyroid mass was positively and significantly correlated with TRAb level ($r=0.406$;$P=0.04$).
Conclusions
In our cohort, the relapse of GD after radioiodine therapy was low (17.1%) and significantly associated with higher FT4 and TRAb levels, heavy thyroid glands and high values of 24 h-radioiodine uptake. Previous treatment with propylthiouracil was related with lower treatment success.

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P1009

Severe side effects of methimazole in the treatment of hyperthyroidism

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Introduction
Methimazole is the thionamide compound most used in the treatment of hyperthyroidism due to its efficacy, commodity and security. Severe side effects are rare, although potentially fatal: agranulocytosis in 0.1–0.5% and toxic hepatitis in 0.1%
Aims
To characterize the patients admitted in the endocrinology ward for the last 10 years for severe complications of methimazole therapy.

Material and Methods
Retrospective analysis of clinical, laboratorial, radiological data, type of therapy and outcome of all the patients admitted in our department between January/2003 and July/2012, using SPSS 21.0®.
Results
Were studied five patients, mean age 68.6±14.9 years. Hyperthyroidism was caused by Graves' disease in three cases, toxic adenoma in one patient and mixed-type amiodarone-induced hyperthyroidism in other patient. Clinical presentation, laboratory, ultrasonography and ^{99m}Tc thyroid scintigraphy compatible with thyrotoxicosis. Patients were treated with 21±6.5 g/day of methimazole for 45.4±22.7 days. Admitted for: leukopenia with relative neutrophilia in one patient(leukocytes=240/μl, neutrophils=64%), agranulocytosis in three patients(mean neutrophil counting=156.6±37.9/μl) and toxic hepatitis in other(AST=353 U/l(30–65), ALT=509 U/l(30–65), ALP=166 U/L(35–104), GGT=269 U/L(5–36)). Clinically: fever without focus in two patients, oropharyngeal and esophageal candidiasis in two cases, septic shock in other patient. Treatment consisted of: methimazole suspension in every patient (n=5), i.v. broad spectrum antibiotics(n=5), i.v. antifungal therapy(n=2), i.v. corticosteroids(n=2), granulocyte macrophage colony-stimulating factor(GM-CSF 30 MUI/day, 5 days)(n=2). Mean duration of ward admition was 20.2±4.1 days; favourable clinical and laboratorial outcome in every case. For hyperthyroidism therapy, three patients received ^{131}I(11.3±4.1 mCI), one patient had spontaneous remission, other patient suspended amiodarone and was started on dexamethasone 48 mg/day with progressive dose reduction. Follow-up after 11.1±4.3 months: four patients euthyroid and one with hypothyroidism after radioiodine therapy, under thyroxine 125 μg/day.
Conclusions
This cohort represents the rarity of methimazole's serious toxicity (five patients in 10 years). However, we stress the severity of the side effects, occurring in an early stage of therapy (45.4±22.7 days). Timely diagnosis depends on close monitoring and high level of clinical suspicion.

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P1010

Proteomic analysis of thyroid tissue in Graves' disease and toxic multinodular goiter

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Introduction
Graves' disease and toxic multinodular goiter are known to have different etiologies and pathogenesis, which are not fully comprehended today. This study compares the protein profiles of Graves' disease and toxic multinodular goiter patients' thyroid samples using proteomics methods and investigates the role of differentiating proteins in the pathogenesis of these diseases.
Methods and Design
Difference Gel Electrophoresis (DIGE) was applied to protein extracts of thyroid samples from 12 patients with Graves' disease and 12 patients with toxic multinodular goiter. Spots with differential expression were revealed by imaging and the proteins were identified by Matrix-assisted laser desorption/ionization time-of-flight mass spectrometer (MALDI TOF) followed by MASCOT search. They were classified on the basis of their functions in metabolic pathways by using Ingenuity Pathways Analysis (IPA).
Results
Difference Gel Electrophoresis images were analysed *via* PDQest Advance software and 330±20 protein spots were detected from the two group of gels. Of these spots, 23 displayed difference in their expressions between Graves' disease and toxic multinodulary goiter samples. These were Prelamin A/C (LMNA), Macrophage capping protein (CAPG), alpha enolase 1 (ENO1), Rho GDP-dissociation inhibitor 1 (ARHGDIA), Peroxiredoxin 2 (PRDX2), Cathepsin B (CTSB), Cathepsin D (CTSD), Apolipoprotein A1 (APOA1), Heat shock protein β1 (HSP β1), Selenium-binding protein 1 (SELENBP1), Creatine kinase B (CKB), Succinyl-KoA:3-ketoacid Coenzyme A transferase 1(OXCT1), Dihidrolipoil dehydrogenase (DLD), Carbonic anhydrase (CA1), Triosephosphate isomerase (TPI1). Ingenuity Pathways Analysis revealed that some of these proteins have functions related to cell proliferation and they were also associated with malignities such as pancreas tumor, hepatocellular carcinoma and colorectal carcinoma.
Conclusion
Although our findings are preliminary, they hold importance by providing the first comprehensive comparative proteomics data about Graves' disease *vs* toxic multinodular goiter.

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P1011

Hyperglycaemia in hypothyroidism

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Thyroid hormones disturbances may lead to glucose metabolism abnormalities but little is known about the risk of hyperglycaemia in hypothyroidism.
The aim of our study is to determine the frequency and the predisposing factors to hyperglycaemia in hypothyroidism.
Subjects and methods
It is a retro and prospective study including 425 hypothyroid subjects (383 F/42 M). We search for hyperglycaemia which means fasting glycaemia ≥;1 g/l and/or glycaemia after OGTT ≥1.40 g/l. Thereafter we search for predictive factors of hyperglycaemia in hypothyroidism.
Results
160 patients (37.6%) had hyperglycaemia. Patients having hyperglycaemia were older (54.4±1.08 vs 45.7±0.8 years), their BMI was higher (31.5±0.53 vs 28.7±0.37 kg/m^2), were more frequently hypertensive (54.3 vs 21.5%) and have more familial background of diabetes (36.2 vs 29.8%) than patients with normal glucose metabolism.
Discussion
It is well known that glucose abnormalities are frequent in hyperthyroidism but little is known about the risk of hyperglycaemia in hypothyroidism. Longstanding hypothyroidism may predispose to hyperglycaemia through the development of abdominal obesity and insulin resistance, ageing patients and patients with familial background of diabetes seems to be at higher risk.

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P1012

May dental extraction trigger subacute thyroiditis?

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Introduction
Subacute thyroiditis (SAT) is a self-limiting thyroid disease associated with a triphasic clinical course of hyperthyroidism, hypothyroidism, and return to normal thyroid function. The well-known clinical features of SAT include thyroid pain with symptoms of hyperthyroidism, suppressed level of thyroid-stimulating hormone (TSH), low thyroid uptake of radioactive iodine, and elevated erythrocyte sedimentation rate. Diagnosis is based on clinical and laboratory data, and tissue diagnosis is rarely required. Here we report about two cases that developed SAT after dental extraction. Most cases of SAT develop after systemic viral infections like Coxsackie, cytomegalovirus, Epstein Barr virus, and adenovirus. SAT (de Quervain's) presents typically with neck pain radiating to the ear. To our knowledge there has been no report about SAT developing after dental extraction. The possible complications of tooth extraction is blood loss, impairment of labial sensation, oro-antral fistula, fracture of the abscesses, endocarditis and bacteremia, but SAT has not been reported.
Cases
Our first case was a 45-year-old woman who experienced fever and neck pain after three days of dental extraction. Her sedimentation rate was elevated and hyperthyroidism was detected. She was started steroid treatment with the diagnosis of SAT. After 1 week her symptoms resolved and her sedimentation rate and suppressed TSH levels returned to normal after 1 month. The second patient was a 44-year-old woman who underwent a dental extraction and experienced neck pain after 4–5 days after the procedure. Her sedimentation rate was elevated and FT_4 level was increased and TSH levels was suppressed.

Her uptake was low which was performed in another hospital. She was started methyl prednisolone and her symptoms resolved after 1 week and laboratory parameters were normal after 6 weeks.
Conclusion
We have observed two cases experiencing subacute thyroiditis after dental extraction.

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P1013

Anti-C1q autoantibodies are linked to autoimmune thyroid disorders in pregnant women.

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Introduction
Anti-C1q antibodies have been implicated in the pathogenesis of systemic lupus erythematosus. We have previously shown that anti-C1q antibodies are also linked to autoimmune thyroid disorders (AITD). The aim of this study was to assess the occurrence of anti-C1q antibodies in pregnant women with AITD.
Methods
Serum anti-C1q antibodies were measured during the 9–11th gestational weeks in 103 pregnant women screened positive for AITD, and in 96 of these women after delivery (median 16 months). As controls, 117 pregnant women without AITD were included. Corresponding serum levels of TSH and free thyroxine (FT_4) were determined. Autoantibodies against thyreoperoxidase (TPOAb) were assessed only in pregnancy.
Results
Anti-C1q antibodies were found more frequently in TPOAb-positive pregnant women than in TPOAb-negative controls (37 vs 12%; $P<0.0001$). Among pregnant women with AITD, TSH levels were higher in the subgroup positive for anti-C1q antibodies than in the anti-C1q-negative subgroup (2.41 vs 1.94 mU/l, $P=0.01$); differences in TPOAb and FT_4 were not significant. TSH positively correlated with anti-C1q antibody levels in all pregnant women ($r=0.20$, $P=0.043$), as well as in the TPOAb-positive subgroup ($r=0.237$, $P=0.027$). Serum levels of anti-C1q antibodies decreased after delivery (12.6 vs 9.4 U/l, $P=0.026$), and did not correlate with thyroid parameters at this time point. Anti-C1q-positivity during pregnancy was not linked to thyroid dysfunction after delivery.
Conclusions
Anti-C1q antibodies are more prevalent in pregnant women with AITD than in healthy pregnant women, but do not associate with postpartum thyroid function.

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P1014

Whether various ways of quality of life answer rank-transformation influence on final score and grouping among hypothyroid patients?

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Quality of life (QoL) of hypothyroid patients can be estimated by use of numerous instruments (GHQ12 and TQ20). By rank transformation of obtained answers, calculated QoL score further determined groups, named as no distress (0–15 patients.), minor distress (16–24 patients.) and major distress ($\geq$25 patients.). Rank transformation can be performed through Likert 0–3 as well modified 0–4 model. To groups with distress, levo-thyroxine (L-T_4) therapy is usually recommended. The aim of study was to calculate different QoL scores and to estimate its effect on distress-grouping.
Methods
Case-control study consisted of 90 patients, divided into three equal groups of 30 participants: treatment-naïve hypothyroid (TSH$>$10 mIU/ml), euthyroid under (L-T_4 substitution and control, euthyroid. TQ20 and GHQ12 were assigned to every study participant. Obtained answers were rank transformed according to mentioned models. Statistical analysis (χ^2, one-way ANOVA, and Kruskal–Wallis) was performed by use of SPSS 18.0.
Results
Mean score of $TQ20_m$, $TQ20_s$, GHQ_m and GHQ_s was 14 ± 7, 13 ± 6, 11 ± 7, and 11 ± 6 respectively and differed between groups. Only one participant in the 'euthyroid' study subpopulation (control+(L-T_4-induced euthyroidism) has had major distress both questionnaire scores, while scores of all others belonged to no distress group. Mean $TQ20_m$, $TQ20_s$, GHQ_m and GHQ_s scores were 21 ± 7, 20 ± 5, 18 ± 6, and 16 ± 5 respectively in the hypothyroid treatment-naïve group and differed in-between group. Minor and major distress $TQ20_m/TQ20_s$ and GHQ_m/GHQ_s scores were registered in 26 (86.7%) and 18 (60%) patients.
Conclusion
Despite subtle differences in absolute values, the scores statistically differed. The values are stressed especially in the treatment naïve hypothyroid group. Highly given scores with modified model, cluster the patients into distress groups and makes the clinician's decision easier regarding (L-T_4 treatment initiation in hypothyroid patients, especially subclinical ones.

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P1015

Differences in genetic predisposition to Graves' disease and Graves' orbitopathy between young and elderly patients

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Background
Graves' disease (GD) is a complex disease in which genetic predisposition is modified by environmental factors. The pathogenesis of GD and Graves' orbitopathy (GO) might have a different genetic background – in some patients GO is observed before or late after diagnosis of GD hyperthyroidism. The aim of the study was to assess genetic predisposition to GD and GO in young patients (age of diagnosis $\leq$30 years of age), in which the time of environmental effects was shorter then in adults and older patients.
Methods
735 GD patients and 1216 healthy controls from Poland were included in the study. 338 of patients had orbitopathy NOSPECS $\geq$2. Association analyses were performed between polymorphisms RTSH, genetic variants in genes encoding proteins involved in immune response: HLADRB1*03, CTLA4, CD40, NFKb, PTPN22 and the age of diagnosis of GD.
Results
The carriers of the HLA DRB1*03 allele were more frequent in patients with age of diagnosis $\leq$30 years then in patients with older age at GD diagnosis. In this young patients the rsl 179247 RTSH was associated with GO. In young GO-free patients, allele A was statistically more frequent and homozygous carriers had a threefold lower risk of disease incidence then patients with AG or GG genotype. Those differences were not found in either elderly patients or the group analyzed as a whole.
Conclusions
HLA DRB1*03 allele is associated with young age at diagnosis of GD.
Allele A of the rsl179247 polymorphism in the RTSH gene is associated with lower risk of GO in young GD patients.

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P1016

Different therapeutic outcomes in two cases with active moderate-to-severe Graves'orbitopathy treated with intravenous steroid therapy-case presentation

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Background
Graves' orbitopathy (GO) comprises mild, moderate-to-severe and severe forms. The treatment is complex, depending on the activity and severity of the disease. Patients with active moderate-to-severe GO benefit by correction of thyrotoxicosis and glucocorticoids (GC), as first-line agents. Approximately 20-40% of cases are not responsive to GC therapy.
Case presentations
There are presented two cases with active moderate-to-severe GO treated with antithyroid drugs (ATD) and GC iv (12 weeks, cumulative dose 4.5 g). After 3 months of therapy, case 1 showed a progression of the disease. The worsening of GO is reflected by: aggravation of current ophthalmic symptoms, alteration of ophthalmic parameters, an increase in CAS score and bilateralization of orbital involvement. Case 2 revealed after the same treatment, an improvement of ophthalmic symptoms and parameters, a decrease of CAS, but no effects on muscle involvement.
Conclusions
The causes of dissociated therapeutic responses in these similar cases were not elucidated. The unsuccessful therapeutic response may elicit: another course of i.v. GC therapy (lower doses), orbital radiotherapy associated with GC (oral and i.v.) or a combination of GC (oral and i.v.) with cyclosporine.

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P1017

Adipokines and cardiovascular risk factors in patients with autoimmune thyroiditis and subclinical hypothyroidism

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Aim
To evaluate the serum levels of resistin and adiponectin, and the potential relationship between these adipokines, thyroid function, lipid profile, C-reactive protein (CRP) and homocysteine levels in patients with autoimmune thyroiditis (AIT) and subclinical hypothyroidism (SCH).
Methods
patients with AIT (58 females; 47.7 ± 16.7 years) were studied; 33 of them had also SCH. These patients were diagnosed by a positive result in an anti-peroxidase (anti-TPO) and anti-thyroglobulin antibodies, and a typical ultrasound pattern. Statistical analyses were done using the Student' *t*-test, Mann–Whitney *U* test, and Spearman's rank correlation test. A two-tailed *P* value <0.05 was considered statistically significant.
Results
The patient subgroups were similar in age and sex distribution. The distribution of overweight (SCH = 40.0 vs 36.7%) and obese (SCH = 31.4 vs 23.3%) patients was not significantly different in the two subgroups. Patients with SCH had significantly higher levels of total (221.3 ± 50.7 vs 199.1 ± 39.3 mg/dl, $P=0.03$) and LDL-cholesterol (137.7 ± 39.3 vs 125.5 ± 57.1 mg/dl, $P=0.02$). In SCH subgroup, FT_4 positively correlated with apoA1 ($r=0.41$, $P=0.04$) and HDL ($r=0.48$, $P<0.01$), and negatively correlated with LP(a) ($r=-0.44$, $P=0.03$). A significant correlation between homocysteine and triglycerides levels was found in patients with SCH ($r=0.58$, $P<0.01$). Both subgroups had similar levels of adiponectin and resistin. In the SCH subgroup we found a positive correlation between resistin and TSH ($r=0.38$, $P=0.03$).
In total group, CRP levels were positively correlated with anti-thyroglobulin ($r=0.33$, $P<0.01$) and resistin levels ($r=0.34$, $P<0.01$). In this group, adiponectin levels positively correlated with HDL-cholesterol ($r=0.3$, $P=0.02$) and resistin positively correlated with triglycerides levels ($r=0.27$, n = 62, $P=0.04$).
Conclusion
Our study suggests that autoimmune thyroiditis, even at its early stages of subclinical hypothyroidism, is associated with an increased cardiovascular risk, given the changes in serum lipid levels and the correlations between thyroid function, CRP, serum lipids and adipokines levels.

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P1018

Oxidative stress in patients with Basedow–Graves' disease

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Basedow–Graves' disease is an autoimmune disorder and the most frequent cause of hyperthyroidism.Increased thyroid hormone concentrations change cellular oxidative metabolism, determining the formation of reactive oxygen species.
Objectives
To study oxidant–antioxidant status and the effect of antithyroid drugs on oxidative stress parameters in Basedow–Graves' disease patients.
Materials and methods
The study was carried out in a group of 23 recently diagnosed, untreated patients with Basedow–Graves' disease. Patients were divided into two groups: control group including 12 women with normal thyroid hormone status without other associated diseases, and a group of 23 patients with newly diagnosed Basedow disease who received antithyroid drugs (AD) and β-blockers for 6 weeks. Malondialdehyde (MDA), protein carbonyls (PC) and reduced glutathion (GSH) were determined from the serum, twice, before the treatment and after 6 weeks of therapy.
Results
The values of MDA, the marker of lipid peroxidation, in patients with Basedow disease at onset were significantly increased compared to those of healthy subjects ($P<0.0001$). After AD and β-blockers administration, MDA values increased insignificantly compared to the group of untreated patients ($P=0.07$). PC levels increased insignificantly in untreated patients with Basedow disease ($P=0.36$) and they also increased without statistical significance after the administration of AD ($P=0.38$). Reduced GSH significantly increased in patients with Basedow disease compared to the control group ($P<0.001$). In patients treated with AD and β-blockers, GSH values increased significantly.
Patients treated with Thiamazol and Metoprolol compared to control patients had significantly increased FT_4 values, decreased TSH values, and significantly increased values of the studied parameters.
Conclusion
The significant increase in MDA, the marker of lipid peroxidation, the increasing tendency of PC and the significant increase of GSH confirm the presence of oxidative stress in patients with hyperthyroidism due to Basedow–Graves' disease. Short-term Thiamazol treatment does not significantly influence the oxidant/antioxidant system parameters in patients with Basedow disease.

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P1019

Oral solution of levothyroxine vs tablets in subclinical hypothyroidism: evaluation of outcomes

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Introduction
Oral levothyroxine (LT_4) is the standard treatment for hypothyroidism and serum TSH represents the best marker for assessing the proper LT_4 dose. The absorption and bioequivalence of different commercial LT_4 preparations might be variable. The aim of this study is to compare the efficacy of levothyroxine oral solution vs tablets.

Methods
Fifty-eight patients (six males, 52 females; average age, 46.9 ± 12.0 years) with primary hypothyroidism receiving LT_4 therapy were recruited at our center between September 2009 and April 2011. The inclusion criteria were as follows: i) age range between 23 and 75 years; ii) patients with subclinical hypothyroidism (TSH level between 2.5 and 4.5 mU), treated with LT_4 oral solution (group O) or tablets (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; iii) use of medications that could potentially interfere with with LT_4 absorption.
Results
TSH significantly decreased in both groups ($P = 0.003$), but repeated-measures ANOVA showed no difference between the two groups ($P = 0.807$). A non significant greater decrease was observed at 3 and 6 month in group O vs group T. Average plasma TSH level was negatively correlated with age ($P = 0.013$) and with BMI ($P = 0.029$). TSH decrease was negatively related to basal BMI, while resulted increased in males vs females.
Discussion
Our preliminary observation seems to show a possible greater efficacy of oral solution, as suggested by the non-significant greater decrease of TSH levels. This finding could be related to the slower absorption rate of tablets vs oral solution, as the latter doesn't need dissolution, before absorption starts. However, prolongation of follow-up is needed to confirm our data.

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P1020

Hématological disorders in hypothyroidism: about a series of 100 cases

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Introduction
Various hematologic disorders have been reported in hypothyroidism. They are resulting from the effect of thyroid hormones regulating the hematopoiesis.
Population and methodology
100 patients with primary hypothyroidism unsubstituted received a thyroid balance (FT_4, TSH us, and Ac anti-TPO cevicale ultrasound) and hematologic exploration (FNS determination of serum ferritin, TIBC). The blood test was completed according to the results. Patients with hematological history or taking a drug that may sound on hematopoiesis were excluded.
Results
63% of patients had hematologic abnormalities: 58% anemia, leukopenia 6%, and 8% thrombocytopenia.
Different types of anemia were objective: normocytic normochromic (34.48%), microcytic (48.28%) Macrocytic (17.24%).
Mean hemoglobin, hematocrit and MCV are respectively 10.2 ± 1.18 g/dl 31, 84 ± 3.97% and 78.4 ± 1.14.
The mean values of white blood cells and platelets are – 150 000 ± 20 and 3000 ± 12. The decrease in the number of white blood cells has focused on neutrophils (70%) and lymphocytes (82%).
Although present in both types of hypothyroidism (moderate and deep), hematological disorders are more pronounced in the second ($n = 38$, mean TSH 15 ± 1.2 mU/l, 60.47%) and (n: 62; TSH average 45 ± 1.2, 64.91%) (P: 0.005)
Paraclinical revaluations 3 and 6 months after hormone replacement showed the complete disappearance of leukopenia and persistence of anemia and thrombocytopenia in 7.7 and 5%. They are due to pernicious anemia and idiopathic thrombocytopenia.
Discussion and conclusion
HT regulate hematopoiesis by acting on erythroblast receptors. They stimulate the secretion of erythropoietin and promote terminal differentiation and proliferation of hematopoietic cells. If thyroid disease, hematological disorders must be research systematically.

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P1021

Vitamin D levels in autoimmune thyroiditis and a control group among the Polish population

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Introduction
Vitamin D, primarily known for its role in calcium–phosphorus homeostasis, is also a significant immunomodulatory factor. Vitamin D deficiency has been reported in some autoimmune disorders. Recently, vitamin D level in autoimmune thyroiditis (Hashimoto's thyroiditis (HT)) has become the subject of researchers' interest.
Objectives
This study aims to assess vitamin 25-OH-D3 levels in HT patients in comparison to a control group in the Polish population. This would be the first attempt conducted in this poor sunlight exposure region.
Patients and methods
The group consisted of 62 subjects diagnosed with HT (mean age 49.15 ± 15.51 and female:male ratio 56:6) and 32 healthy controls matched with age and sex (mean age 46.09 ± 14.32 and female:male ratio 28:4). All blood samples were collected in the first quarter of the year to minimize the impact of seasonal fluctuations of vitamin D concentrations.
Results
In the HT group the mean vitamin D level was 20.09 nmol/l (S.D. ± 12.66), compared to 30.31 nmol/l (S.D. ± 19.49) in the controls, $P = 0.014$. All the patients and controls were insufficient (according to the normal level – a serum concentration between 75 and 125 nmol/l). The deficiency (vitamin D < 50 nmol/l) was significantly more common among HT patients compared to the controls (61–98.4 vs 27–84.4%), $P = 0.029$.
Conclusions
Statistically significant difference in serum vitamin D concentrations between patients with HT and the control group has been found in our study, which is in accordance with the literature. This may suggest vitamin D deficiency is one of the environmental factors in HT development, although further studies are needed to confirm these observations.
Keywords
Autoimmune thyroiditis, vitamin D, etiopathogenesis, autoimmunity.

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P1022

Abstract withdrawn.

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P1023

Is Clinical Activity Score (CAS) a sufficient indicator of the response to therapy with i.v. methylprednisolone (MP) and external radiotherapy (RT) for Graves orbitopathy?

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Introduction
Treatment of Graves orbitopathy (GO) is one of the most difficult problems in clinical endocrinology.
Objective
To establish the efficacy of the regime used in the treatment of GO and to analyze methods used to determine treatment effectiveness.
Material
The study involved 30 patients with moderate to severe GO (according to the classification of EUGOGO) being in the active phase of GO.
Method
Patients were treated with weekly infusions of MP (6×500 mg+6×250 mg), and with RT (1 Gy/day–for 10 days in weeks 7 and 8). Before and after treatment each patient underwent clinical examination with clinical activity score (CAS), ophthalmologist examiation with determining exophtalmos (Hertel), MRI examination of retrobulbal region determining the number of muscles involved, their thickness, activity and radiological degree of exophthalmos. The severity of diplopia has been determined subjectively by the patients. Results were compared in groups: responders (RESP) and non-responders (NON-RESP).
Results
We found:
i) a reduction (normalization) in CAS in all patients (mean reduction rate of 2.5 points in RESP, and of 2.4 in NON-RESP).
ii) Statistically significant reduction in the severity of diplopia, exophthalmos (Hertel and MR), number and thickness of involved muscles in RESP group compared to no statistically significant reduction in these parameters in NON-RESP group.
iii) Inflammatory activity in extraocular muscles has normalized in all patients from the RESP group (normalization of T2 time signal in MRI), in contrast to the lack of normalization in the NON-RESP group.
Conclusions
i) In our opinion, the normalization of CAS does not always indicate a sufficient clinical response to treatment with above regime (MP+RT).
ii) If measured only by CAS the treatment regime reaches 100% efficacy. After joining the results of ophthalmological examination, MRI, and subjective assessment of the diplopia, the efficacy decreases to 80%.

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P1024

A case of thyrotoxic hypokalemic periodic paralysis presenting with 'U' wave on ECG

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Introduction
Hypokalemic periodic paralysis (HPP), is a rare neuromuscular disorder caused by dysfunction of the ion channels in red muscle cells which is characterized by painless episodes of muscle weakness generally after strenuous exertion or a high-carbohydrate meal. However, some HPP patients secondary to thyrotoxicosis are also described.
Case
A 41-year-old Caucasian man, without any chronic disease, presented to our emergency department with generalized muscle weakness pronounced in his both upper and lower extremities. He recalled many similar but milder episodes in the previous 2 months. The physical examination made by a neurologist had no pathology but only quadriparesis. His initial potassium level was 1.5 mEq/l on admission and his electrocardiogram showed an obvious U wave (Figure 1). An initial diagnosis of hypokalemic periodic paralysis was made and he was immediately given intravenous potassium chloride in the emergency department. It was learned that he had no family history and he had a high-carbohydrate diet a few hours before the quadriparesis occurred. Physical examination revealed a slightly enlarged thyroid gland without nodules and exophthalmos was present. TSH level was <0.03 μU/ml (0.25–5.0), fT_4 level 4.21 ng/dl (0.77–1.71), and fT_3 19.55 ng/dl (0.23–0.39). Under these findings, the patient was diagnosed as having thyrotoxic hypokalemic periodic paralysis associated with Graves' thyrotoxicosis and treatment with methimazole was initiated. Serial measurements of his serum potassium level which was too low on admission and then became normal after administering intravenous potassium chloride, remained within normal limits without any oral potassium supplements in the hospital. Treatment with propranolol was also initiated as 4×40 mg/day.
Discussion
The pathogenesis of THPP is the activation of Na^+/K^+-ATPase pump because of hyperinsulinemia, increasing of thyroid hormones and beta-adrenergic stimulation. Therefore, B receptor blockage, anti-thyroid drugs and low-carbohydrate meals are recommended for treatment and prophylaxis of THPP.

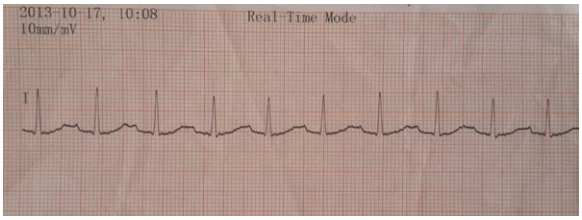

Figure 1

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P1025

Does radioactive iodine ablation treatment in patients with hyperthyroidism effect on glucose metabolism?

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Aim
Radioactive iodine (RAI) ablation therapy is used as part of the treatment for hyperthyroidism. Recently, low dose applied ^{131}I treatment for hyperthyroidism has decreased the need for thyroidectomy. The aim of this study was to evaluate serum fasting glucose (FG) values in pre and post treatment RAI patients.
Materials and Methods
Thirty-two patients with hyperthyroidism (mean age 56.0±14.5 years; range 24–83) treated with a single therapeutic dose of ^{131}I (range 8–15 μCi) in our endocrinology department between 2009 and 2013 years were included this study. Before ^{131}I administration, one patient had subclinical hyperthyroidism and 31 patients had overt hyperthyroidism. Post treatment follow-up ranged from 1 to 4 years for long-term effect of RAI treatment. Clinical and biochemical assessment with FG, lipid profile, free T_3, free T_4 and TSH were performed approximately every 3 months during the first year and at longer intervals afterwards. All these parameters were reevaluated at least after 1 year post treatment.
Results
Before RAI treatment mean free T_3 levels was 4.6±1.5 pg/ml; mean free T_4 levels was 1.5±0.7 ng/dl; TSH levels was 0.1±0.2 μIU/ml; FG levels was 95.1±20.2 mg/dl; LDL-cholesterol levels was 108.6±39.5 mg/dl. After RAI treatment the free T_3 levels was 3.07±0.5 pg/ml; free T_4 levels was 1.1±0.2 ng/dl; TSH levels was 1.6±1.3 μIU/ml: FG levels was 121.5±48.2 mg/dl; and LDL-cholesterol levels was 122.6±31.7 mg/dl. Serum fasting glucose and LDL-cholesterol levels after the RAI treatment were significantly different from pretreatment levels ($P=0.002$ and $P=0.043$ respectively).

Conclusions
We demonstrated that glucose metabolism in the patients with hyperthyroidism might be impaired after RAI ablation treatment despite exposure to limiting dose of the radiation. We suggest that serum fasting glucose levels must be more carefully follow-up after RAI ablation treatment. There is a need for further prospective study which was clarified relationship between serum fasting glucose and RAI therapy.

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P1026

Nutriciological monitoring of iodine status as a measure of iodine deficiency prevention

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Implementation strategies for the elimination of iodine deficiency in the last 10 years in Belarus has achieved the WHO evaluation criteria. This was made possible by the universal use of iodized salt in food manufacturing, food service of all types and the availability of its free-trade network salt addition.
The aim of this work was to study the iodine daily intake from food, as one of the measures to monitor iodine supply of the population.
In assessing iodine intake used two criteria: recommended daily intake (150 μg) and safe upper intake level (1100 μg/day). The calculation was performed as quantities mg (μg)/kg body weight/day, based on a standard body weight of 60 kg.
Results
Using foodstuff of an intra country origin shows, that intake of iodine looks as follows: the highest iodine content was in bakery products (in 162.7 g contains 64 μ of iodine), sausage products (in 50 g – 64.1 μ of iodine), dairy products (in 280 g – 54.1 μ of iodine), vegetables (17.2 μ of iodine in 430.5 g of vegetables). Fish products consumption at level 14 g/day in an organism enters 10.4 g of iodine. 162.7 g of grain contains 10.2 μ iodine, in 112.9 g of meat of −7.5 g and 98.3 g of potatoes – 4.9 μ of iodine respectively. Considerably the smaller amount of iodine contains in such products as eggs (in 10.5 g – 2.9 μ of iodine), fruit (in 124.7 g – 2.7 μ iodine), sugar and confectionery (in 45.8 g – 2.5 μ of iodine). The smallest amount of iodine, only 0.5 μ contains in 23.4 g of juice and 7.5 g of alcoholic beverages.
Conclusion
Consumption of 10% of foodstuff in a diet enriched with iodine in industrial conditions even without iodated salt use allows to provide physiological requirement for adults. This results confirm efficiency of national strategy chosen in Republic of Belarus for elimination of iodine deficiency.

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P1027

DHEAS Levels in Obese Patients with Hashimato Thyroiditis

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Introduction
It is well known association between cardiovascular disease and PCOS. Approximately 17–43% of women with PCOS have hyperprolactinemia. Increased levels of prolactin often associated with an increased risk for thromboembolic events, but underline pathophisiological mechanism still unknown. The strong association between hyperprolactinemia and platelet aggregation is well known. Platelets play a key role in the development of atherothrombosis, a major contributor of cardiovascular events. Mean platelet volume (MPV) is a marker of platelet size that reflect to activity of the platelet. MPV is easily determined on routine hemogram analysis at a relatively low cost. Larger platelets with higher MPV values are hemostatically more reactive and produce higher amounts of the prothrombotic factor.We also investigated the relationships between serum PRL levels and MPV levels in subjects with PCOS.
Design/methods
We conducted consecutively subjects with PCOS who have higher prolactin levels ($n=72$) and who have normal prolactin levels ($n=207$) and subjects without PCOS ($n=90$).
Results
MPV levels were significantly higher in PCOS subjects with elevated prolactin levels compared to both in PCOS with normal prolactin levels and control groups ($P<0.001$). MPV levels were positively correlated with prolactin levels ($r=0.387$, $P<0.001$), free testosteron levels ($r=0.135$, $P=0.010$) and negatively correlated with platelet counts ($r=-0.333$, $P<0.001$). Furthermore, multiple regression analysis showed that prolactin levels were directly related to MPV levels ($R^2=0.239$, $\beta=0.354$, and $P<0.001$).
Conclusions
In the present study we showed that increased prolactin levels cause increased MPV levels in PCOS and results of multiple regression analysis showed that prolactin levels were directly effected to MPV levels independent from other factors. This implies a higher risk of hypercoagulability and therefore an increased risk of future cardiovascular disease in pcos subjects wiht eleveted prolactin levels.

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P1028

The role of peroxisome proliferator-activated receptors α polymorphisms in Graves' disease and orbitopathy

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Understanding the genetic etiology of Graves' disease (GD) and Graves' orbitopathy (GO) is recognized as an urgent priority. Since peroxisome proliferator-activated receptors α (PPARα) exhibit anti-inflammatory and immunomodulatory activity, and are required for the control of the adipose inflammation process their role in the GD and GO pathogenesis has been proposed. Abnormal expression and/or function of PPARα could suppress the inflammatory response by direct up regulation of gene(s) with anti-inflammatory properties.
Three SNPs within PPARα gene: rs135551 (c.−127+5148A>G), rs1800206 (c.484C>G), (Leu162Val) and rs4253766 (c.712-3784C>T) were investigated in 276 Polish Caucasian GD patients in the context of presence, activity and severity of GO, as well as familial history of thyroid disease, response to the anti-thyroid treatment and gender or smoking status. SNPs were determined with use of the allelic discrimination methods.
Although, univariate analysis did not found any association with risk of GO as well as with its activity or severity we found a specific haplotype rs135551(G)/rs1800206(G)/rs4253766(C) which 3.47 times increase the risk of severe GO ($\chi^2=5.10$, $P=0.02$). Moreover the same haplotype was statistically significant more frequent in smokers (OR=7.73, $\chi^2=4.77$, $P=0.03$) as well as 4.17-times increased the risk of severe GO ($\chi^2=6.81$, $P=0.009$) whereas haplotype rs135551(A)/rs1800206(G)/rs4253766(C) significantly decreased the risk of severe eye symptoms (OR=0.013, $\chi^2=4.43$, $P=0.04$). Additionally, univariate analysis showed a trend toward increased frequency of rs135551 (GG) genotype ($P=0.06$) and (G) allele ((GG) and/or (GC) genotypes) ($P=0.08$) in smokers. Furthermore, there was also a trend toward increased frequency of rs13551 (A) allele ((AA) and/or (GA) genotypes) and haplotype rs13551(G)/ rs1800206(C)/ rs4253766(C) in responders to anti-thyroid treatment ($P=0.07$

and $P=0.07$ respectively). The rs13551 (GG) genotype was statistically significantly increased in patients without familial background (OR = 1.75, $P=0.04$) but haplotype rs13551(A)/ rs1800206(G)/ rs4253766(C) was 106.42 times more frequent in patients with familial history of thyroid disease ($\chi^2=3.65$, $P=0.05$).

Our association study suggests that PPARα polymorphisms may be involved in the pathogenesis of GD and GO.

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P1029

Mediastinal goiter: a rare cause of dyspnea, chest and back pain

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Primary mediastinal ectopic goiters are very rare and comprise about 1% of all mediastinal tumors. Blood supply of primary mediastinal goiter comes from local intrathoracic vessels. Compressing symptoms, diagnostic uncertainty, and the risk of malignancy support surgical excision.

Case report

The patient is a 40-year-old woman with a 6-month history of progressive dyspnea, chest and back pain. Chest X-ray showed the left superior mediastinal mass was compressing the trachea. A computed tomography (CT) scan confirmed a posterior mediastinal (retrotracheal visceral mediastinum) mass with cervical connections. Thoracic biopsy was performed and pathology was colloidal goiter. Hematological and chemistry panels were normal. A left posterolateral thoracotomy was performed. The mass was, behind the arcus aorta, left carotid and subclavian arteries. Although the mass was pushing the trachea through the right hemithorax, there was no invasion. On the other hand, the esophagus was compressed to the right and posterior aspect of the thorax. There was a 13 cm contact between the columna vertebrales and the mass. The specimen was solid, and measured 13 × 11 × 10 cm. Histological examination was representative of colloidal goiter.

Discussion

Ectopic intrathoracic thyroid is a rare presentation of thyroid disease and comprises about 1% of all mediastinal tumors. The anterior mediastinum makes up 75–94% of intrathoracic goiters. The posterior mediastinal masses constitute 10–15%. The right posterior mediastinum is the most common location, in which the aortic arch development blocks descent to the left. Symptoms at presentation vary and range from minimal to disabling. These include cough, pain, neck swelling, dysphagia, superior vena cava syndrome, or dysfunction of the recurrent laryngeal nerve. Our patient has admitted to our clinic with progressive dyspnea and stridor.

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P1030

Infliximab-induced destructive thyroiditis followed by hypothyroidism: a case report

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Introduction

Infliximab is a tumour necrosis factor (TNF) α inhibitor and used for the treatment of psoriasis. Herein, we report a case of destructive thyroiditis accompanied by transient thyrotoxicosis resulting from the infliximab therapy for the treatment of psoriasis.

Case report

A 57-year-old man suffered from psoriasis and was treated with infliximab therapy for 4 years. Thyroid function tests were normal before infliximab therapy. When the patient presented in our clinic, he had thyrotoxicosis and was using propylthiouracil. The ^{99m}technetium-pertechnetate thyroid scintigraphy showed no visualization of both thyroid lobes and decreased thyroid iodine uptake. TSH receptor antibody, thyroperoxidase antibody and thyroglobulin antibody were negative. Thyroid ultrasonography revealed a heterogeneous thyroid gland (5.5 × 1.7 × 1.5 cm of the right lobe and 4.3 × 1.4 × 1.0 cm of the left lobe) without nodule. After stopping of propylthiouracil therapy, he advised to monitor his thyroid function tests in the following weeks and infliximab therapy for psoriasis was continued. Four weeks later, his thyroid function tests showed elevated TSH level with a normal free T_3 and T_4 levels and levothyroxine treatment was administered to the patient. Thyroid function tests normalized after levothyroxine treatment. One year later, infliximab therapy was stopped because of clinical remission. Simultaneously, levothyroxine treatment was also stopped. His thyroid function were normal 6 weeks after the cessation of levothyroxine treatment.

Conclusion

To our knowledge, the present case is the third infliximab-induced transient destructive thyrotoxicosis followed by hypothyroidism. Therefore, periodic follow-up of thyroid function tests is necessary during infliximab therapy.

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P1031

An increase in the circulating concentrations of triiodothyronine appears to be a function of the peripheral conversion of tetraiodothyronine by deiodinases instead of increased stimulation by thyroid stimulating hormone at puberty in normal healthy boys

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Thyroid stimulating hormone (TSH) causes synthesis of 90% of pro-hormone tetraiodothyronine (T_4) and 10% of active triiodothyronine (T_3) from thyroid gland. T_3 regulates energy metabolism, thermogenesis, body temperature and normal brain development. T_3 is produced from deiodination of T_4 and circulating levels of T_3 are regulated by deiodinases in response to body's needs. The peripheral conversion of T_4 to T_3 by determining age and pubertal stage dependent changes in circulating concentrations of TSH, T_4 and T_3 in boys ($n=671$) of 1 to 20 years was investigated. Blood samples were collected and concentrations of TSH, T_4 and T_3 were determined. Data were analyzed using Student's t test, anova and Pearson correlation. The concentrations of TSH increased to a peak at 5th year, remained low till 9th year, exhibited a 2nd peak at 12th year and later showed peaks at alternate years. The concentrations of TSH were higher at infancy, increased at prepuberty, declined at early puberty and showed a peak at mid puberty. The levels of T_4 were higher during 1st nine years, slightly increased during 14th and 15th years and decreased to lower levels by 20th year. The concentrations of T_3 were low during first eight years, increased progressively reaching peak levels at 17th year and maintained by 20th year. The peripheral conversion of T_4 to T_3 was low as high concentrations of T_4 and low of T_3 were observed during first decade. The plasma concentrations of T_4 kept on decreasing and those of T_3 kept on increasing during second decade. The concentrations of T_4 gradually declined from infancy to late puberty/adolescent, whereas those of T_3 progressively increase from prepuberty to late puberty/adolescent. In conclusion, the present study indicates that the activity of diodenases increases at puberty causing greater conversion of T_4 to T_3 in response to increased metabolic demand.

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P1032

Interplay between ghrelin, obestatin, leptin and triiodothyronine that possibly regulate energy metabolism during the time of puberty in normal healthy boys

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Ghrelin, a putative signal of insufficient energy stores, increases in fasting states, decreases postprandially, and acts as a potent appetite stimulant increasing food intake. Obestatin affects appetite, food preferences to increase daily caloric intake and weight gain. Leptin regulates body fat mass, food intake and energy expenditure. Triiodothyronine (T_3) is a determinant of adiposity, thermogenesis, glucose and lipid metabolism, appetite, food intake, and the oxidation of fatty acids. The present study explored interplay between circulating concentrations of ghrelin, obestatin, leptin and T_3 in boys ($n=529$) between the age of 10 and 20 years. Blood samples were collected and plasma concentrations of ghrelin, obestatin, leptin and T_3 were determined using specific ELISA. Data were analyzed using Student's *t*-test, ANOVA and Pearson's correlation. The concentrations of ghrelin significantly increased at 11th year of age, sustained till 13th year, abruptly increased at 14th year markedly decreased till 16th year and significantly augmented to peak concentration at 17th year, and declined at 18th year and maintained at 19th and 20th years. The concentrations of obestatin suddenly augmented at 11th year, increased steadily till 14th year, markedly rose reaching peak concentrations at 17th year, at 18th, 19th and 20th years. The levels of leptin markedly and progressively declined to lowest concentrations at 18th year and significantly increased at 19th and 20th years. The concentrations of T_3 progressively and markedly increased to peak concentrations at 17th year, thereafter slightly decreased and sustained at 20th year. The concentrations of ghrelin, obestatin and T_3 increased, whereas the levels of leptin decreased during mid puberty. The concentrations of ghrelin were maintained, those of obestain and leptin declined but the concentrations of T_3 increased during late puberty/adolescence. The concentrations of ghrelin, obestatin and T_3 were positively correlated with one another and negatively correlated with leptin at mid puberty.

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P1033

Obesity and metabolic syndrome in patients with primary acquired hypothyroidism undergoing chronic LT_4 replacement therapy

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Hypothyroidism is a risk factor for obesity, central adiposity and ectopic fat accumulation. To assess whether this risk could be detected also in stable patients taking regularly the LT_4 replacement therapy we assessed retrospectively the prevalence of metabolic syndrome (ATP III definition) and calculated the fatty liver index (FLI) and the visceral adiposity index (VAI) in patients attending our Outpatient Endocrinology Clinic because of known primary acquired hypothyroidism undergoing LT_4 replacement therapy on a regular basis ($n=997$) and used as control group patients with stable euthyroid multi-nodular goitre (MNG; $n=502$). Hypothyroid patients were younger (56 ± 15 vs 60 ± 14 years; $P<0.001$), and showed higher BMI (28.7 ± 6.4 vs 27.2 ± 5.3 kg/m^2; $P<0.001$) and FLI (58 ± 31 vs 49 ± 32; $P=0.02$) but no difference in VAI (4.6 ± 3.1 vs 4.6 ± 3.5) and prevalence of the metabolic syndrome (47 vs 47%), neither in the prevalence of type 2 diabetes (11 vs 11%) and known CVD (11 vs 12%) when compared to MNG patients. The actual BMI was directly associated with the duration of LT_4 replacement therapy also when adjusted for age, sex and average TSH levels ($R=0.30$; $p=0.03$). No difference in metabolic syndrome, FLI and VAI was detected when the comparison between groups was adjusted for age, sex and BMI. In conclusion, hypothyroid patients regularly undergoing LT_4 replacement therapy showed higher BMI regardless of age, sex and TSH levels in comparison with MNG patients. In contrast, no difference in the prevalence of the metabolic syndrome and in surrogate biomarkers of fatty liver and visceral adiposity was observed when the analysis was adjusted for the different age and BMI. The isolated finding of higher BMI may be due to an initial weight gain associated to the diagnostic-related delay in beginning LT_4 therapy but also to persistent subtle defects of energy metabolism not fully reverted by the LT_4 therapy.

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P1034

A descriptive study on individually titrated levothyroxine in the management of South African hypothyroid patients (DeuTSH)

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Background
Currently little data regarding hypothyroidism in South Africa exists, but it can be seen from international literature that a significant amount of patients, fail to reach target TSH levels.
Objectives
This observational study aimed to measure the efficacy of individually titrated doses of levothyroxine to achieve a euthyroid state.
Methods
Patients with hypothyroidism, treatment naïve and insufficiently controlled, confirmed with a laboratory TSH value, were included in the study Patients were followed-up every 7 weeks until target TSH values were achieved. Total study duration for patients not reaching target TSH levels, was 28 weeks. TSH levels, levothyroxine dose changes, compliance, concomitant medication used, weight and changes in typical disease symptoms were assessed at each visit.
Results
290 evaluable patients were enrolled. Overall 221 (76.2%) patients reached TSH target levels of which 135 (46.6%) reached control at visit 2. 34 (11.7%) of patients were overtreated. The mean daily dosage per kg/body weight for patients achieving a euthyroid state was 1.12 µg/kg (S.D. 0.54). and the mean daily dosage 88.8 (S.D. 43.2). The most frequently used dosages in treatment naïve patients were 50 or 100 µg, whilst in pre-treated patients it were 75 and 100 µg. The 25 µg thyroxin dosage was used in 46.4% of patients and the, 12.5 µg dosage in 8.2% of patients.
Conclusions
This study highlights the need of an initial early follow-up of TSH values and continued regular monitoring until control is achieved. Potential complications of overtreatment such as osteoporosis, cardiac dysrhythmias, etc. can be devastating to patients and should be addressed amongst treating physicians. This study further highlights that a high proportion (50%) of patients required the 25 and 12.5 µg dosages for optimal titration. The mean thyroxin dosage of 1.12 µg/kg body weight in controlled patients is lower than the recommended 1.6 µg/kg.

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P1035

Results of preventive radioiodine therapy in euthyroid patients with history of hyperthyroidism prior to administration of amiodarone with permanent atrial fibrillation (preliminary study)

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Introduction
Radioiodine (RAI) therapy is a standard procedure in therapy of hyperthyroidism. However, the use of RAI in euthyroid patients requiring chronic administration of amiodarone (AM), in a case of lacking efficacy of other antiarrhythmic drugs might be controversial.

Objective
The aim of the study was to assess the safety and efficacy of an AM therapy prior to treatment with radioiodine therapy in euthyroid patients with permanent atrial fibrillation (PAF), who were treated for hyperthyroidism in the past.
Patients and methods
This was a retrospective observational study. Patients were assessed at baseline and 2, 6, 8, and 12 months after RAI therapy. 17 euthyroid patients with PAF were qualified to the RAI (female/male 3/14; range age from 65 to 87, median 71 years). The patients required chronic administration of AM as a prophylaxis against sudden death.
Results
Each patient received an ablative dose of 800 MBq (22 mCi) of ^{131}I. At the baseline and the time of observation no side effects of the therapy and no signs of drug intolerance were observed. Subclinical hyperthyroidism occurred in 2 (11.8%) cases after 2 months of RAI and 5 weeks of AM administration. In this situation RAI therapy was repeated. Three patients (17.6%) after 6 months and another 2 (11.8%) after 8 months required submission of additional dose of ^{131}I due to amiodarone induced thyrotoxicosis (AIT). Twelve patients (70.6%) returned to spontaneous sinus rhythm within 2 months. Fourteen patients (82.4%) had sinus rhythm during follow-up after 6 and 12 months of treatment.
Conclusions
Prevention of RAI therapy before including AM in euthyroid patients (but previously hyperthyroid), with PAF when other antiarrhytmic drugs are ineffective may be a method of choice. This is particularly important for patients who will require permanent AM administration as a life-saving drug.

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P1036

A case with suppurative thyroiditis caused by salmonella infection

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Introduction
Non-typhoid salmonella as the causative agent of acute bacterial thyroiditis is rarely reported. We report a case with suppurative thyroiditis caused by salmonella infection.
Case report
Fifty-year old woman had fewer and recurrent pain with swelling in the left region of the neck. Physical examination revealed the weight 78 kg, the height 167 cm, blood pressure 100/70 mmHg, pulse 78/min, the body temperature 37.6 degrees. Thyroid gland was stage 3 with lobulated. In sonography evaluation, the left lobe was ~ 5–6 cm in size and lobulated with cystic lesion. The images of the computed tomography was shown the heterogeneous-hypodense images in the left lobe of the thyroid ~ 5×4.5 cm in size. Trachea was deviated slightly to the right. The eritrosit sedimentation rate and the level of C-reactive protein were 52 mm/h and 115 mg/l respectively. Thyroid function tests and autoantibodies were normal. Fine-needle biopsy samples including purulent materials were aspirated. Surgical drainage was performed. In the tissue culture, 100 000 CFU/ml *Salmonella* spp. were detected. The patient's symptoms and findings were completely recovered with ciprofloxacin and metronidazole during 4 weeks.
Discussion
Acute suppurative thyroiditis very rarely can cause the thyroid gland cases. Especially our data in patients as well as acute suppurative thyroiditis should be considered, with or without underlying immunosuppressive condition, neck pain and swelling is reached with subacute thyroiditis, bleeding into cysts and cancer. Acute suppurative thyroiditis in charge, salmonella infection should be kept in mind though very rare.

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P1037

Grave's disease as an adverse effect of ipilimumab: first description of two cases

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Ipilimumab is an immunomodulating agent for the treatment of metastatic melanoma. Ipilimumab is a human mAb which works by inhibiting cytotoxic T-lymphocyte antigen 4 (CTLA-4).
CTLA4 typically works to down-regulate the T-cell response and protects self-antigens from recognition by the immune system. Since the T-cells are no longer down-regulated by this antigen, they are allowed to proliferate, thereby helping to prevent melanoma tumor evasion. As a result of the up-regulation of the immune system, immune-mediated adverse effects have been reported including colitis, dermatitis, hepatitis and hypophysitis. Typically, these effects are treated with high-dose steroids and most eventually resolve.
We present two cases of female patients referred to our department with manifestations of hyperthyroidism. They were 66 and 61 years old without autoimmune background. Hyperthyroism ocurred 1 month after their fourth dose of ipilimumab for metastatic malignant melanoma. Hyperthyroidism was initially controlled by steroids but with recurrence 2 and 4 months respectively after the beginning of steroid therapy. Clinical, biological presentation was usual with elevated TRAK. Curiously, there was no hypervascularization at presentation but only at recurrence.
There have been no reported cases of Grave's hyperthyroidism with ipilimumab therapy to our knowledge but only two cases of euthyroid ophtalmopathy. We discuss the presentation of these cases in the light of classical Grave's diseases and previous reports of autoimmune endocrinopathies.

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P1038

Thyroglobulin as a biomarker of iodine deficiency

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Introduction
We are presenting our results on the relationship between a concentration of urinary iodine (UI) and serum thyroglobulin (Tg) in population studies carried out on a general healthy total population that was randomly selected (individuals aged 6–98 years, 1751 males, 2420 females). 87.2% of the total population was described as the normal population with a simultaneously determined thyrotropin and free thyroxine within reference ranges.
Methods
The individuals were divided into subgroups with moderate and mild iodine deficiency, adequate, more than adequate and excessive iodine intake. The mean and median of Tg were calculated in these subgroups.
Results
Tg concentrations were dependent on gender, age and UI. Upper nonparametric tolerance limits of Tg in relation to iodine intake were calculated from individuals of the normal population, in which both the concentration of Tg and urinary iodine were within the normal reference range (Tg = 0–85 μg/l, UI = 100–200 μg/l). Tolerance limits were dependent on gender and age. The total value of tolerance limits is 44 μg/l; for individuals aged 6–17 years it is 39.1; 18–65 years = 51.4 and 66–98 years = 60.6 μg/l.
Conclusion
Tg seems to be a useful marker of iodine deficiency in a population, in which thyroid diseases are not too frequent. Our results also show that, under conditions of iodine deficiency, insufficient iodine intake is a factor that increases the concentration of Tg in the circulation and thus directly points to the fact that thyroid disorders are amplified by iodine deficiency. Children and the elderly are more affected. In general, Tg serum concentrations higher than 40 μg/l should be an indicator for determining urinary iodine.

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P1039

Abstract withdrawn.

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P1040

Quality of life and the psychoemotional status of the patients after radical treatment of Graves' disease

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Methods
157 patients (118 women and 39 men) aged from 30 to 73 years with radical treatment for Graves' disease were included in this study. Patients were divided into two groups depending on a type of radical treatment: 76 patients have received radioiodine therapy, 81 persons received surgical treatment. Quality of life assessment was made by SF-36 questionnaire which includes eight scales: (physical functioning (PF), role physical functioning (RPF), pain (B), general health (GH), vital activity, social functioning (SF), role emotional functioning (REF), mental health (MH). The psychoemotional status was assessed by Spielberg-Khanin's test and beck depression scale.
Results
Groups were comparable on a sex, age, period of follow-up after treatment, TSH levels, dose of levothyroxine. The median of indicators of Q&L on eight scales of the questionnaire in group of radio iodine fluctuated from 33.3 (role emotional functioning) to 62.5 (social functioning), points on a scale of a depression made 16 (13.5; 19), situational alarm 41.5 (36.5; 45), personal alarm 44 (36.5; 46). The median of indicators of Q&L in group with surgical treatment fluctuated from 40.8 (vital activity) to 62 (pain). Points on a scale of a depression made 15 (12; 18), situational alarm 44 (25; 60), personal alarm 44 (31; 67). There were no significant differences on all scales of a SF-36 questionare, level of alarm and a depression ($P > 0.05$). However almost all indicators of quality of life in both groups were below average level, which can be caused by hypothyroidism.
Conclusion
Indicators of quality of life and the psychoemotional status of the patients who have received different types of radical treatment of Graves' disease doesn't depend on a type of radical treatment.

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P1041

The induction of hyperthyroidism in patient with non-toxic goiter after radioiodine therapy: a case report

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Two female patients aged 44 (PtA) and 68 years old (PtB) with non-toxic nodular goitre for more than 10 years were treated with radioiodine therapy. High resolution ultrasonography show enlarged thyroid glands 50 ml, with two nodules in left and right lobe in PtA and 58 ml with one nodule in the left lobe in PtB. Serum TSH, fT_4 and fT_3 were in normal ranges. Malignancy was ruled out by ultrasound-guided fine-needle aspiration biopsy. In PtA thyroid radioiodine scintigraphy showed homogenous and diffuse uptake, with 33% radioiodine uptake (RAIU) after 24 h; and homogenous uptake, with 32% RAIU in PtB. The effective half-life was 7 days for both patients. The activity dose was calculated by Marinelli's formula and PtA received 280 MBq and PtB receive 600 MBq of I-131. Follow-up control was done every 4 weeks. Hyperthyroidism was induced after 3 months of radioiodine therapy in PtA and after 5 months in PtB. TSH serum levels decreased and serum FT_4 and FT_3 increased. The levels of TSH receptor antibodies were positive in both patients, the anti thyroglobulin and anti peroxidase antibodies were within normal range. thyroid scintigraphy showed homogenous and diffuse uptake in both lobes with small reduction in the thyroid volume. RAIU after 24 h was 53% for PtA and 48% for PtB. Both patients received antithyroid drugs to control the hyperthyroidism. After 6 months of radioiodine therapy both patients received second dose of radioiodine therapy 400 MBq each. After 3 months of the therapy PtA developed hypothyroidism and PtB was in euthyroid state. Radioiodine therapy is non-invasive, safe and cost effective method of therapy for reduction of goitre even in patient with low radioiodine uptake. In these cases radioiodine therapy induce hyperthyroidism, this may be due to the activation of silent Graves' disease in these patients.

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P1042

Antithyroid drug-induced agranulocytosis: experience of the French centers of Pharmacovigilance with a retrospective study of more than 200 cases

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Objective
Agranulocytosis to the antithyroid drugs is a rare adverse drug effect exposure to potentially lethal infections. It is a public health problem with hyperthyroidism in nearly 1% of the French population. However, many uncertainties remain in the knowledge, understanding, prevention and management of this drug effect. In this work, we report the French experience through pharmacovigilance data.
Materials and methods
This is a retrospective study between 1980 and 2006 including 203 patients with documented agranulocytosis in one of three French licensed antithyroid drugs: carbimazol, benzylthiouracil, propylthiouracil. These patients were selected from the national pharmacovigilance database. Data were analyzed and compared to the literature. Data were also analyzed according to the use or not of hematopoietic growth factors (G-CSF).
Results
This study is one of the largest series ever collected on antithyroid drug-induced agranulocytosis. It primarily concerns carbimazol, leader antithyroid drug used in France. It was noted an almost bimodal distribution with women over 65, but also young women aged 20–35 years. This distribution was explained by the fact that the majority of patients treated with antithyroid drug have Graves' disease. Often nonspecific clinical presentations and low contribution of microbiological investigations highlight the difficulties of management. This adverse drug exposed to the often serious infectious complications and death in 8% of cases. Duration of agranulocytosis, neutropenia and hospitalization are very close if not superior in the group treated with G-CSF. Univariate analyzes showed no statistically significant association between the use of G-CSF and duration of agranulocytosis. Mortality was not statistically significant decreased in the G-CSF group: 4.6 vs 12.9%.
Conclusion
The data of this work and a critical review of the literature lead to useful practical recommendations for the prevention and the diagnostic and therapeutic management of this adverse drug effect.

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P1043

Quality of life of patients with hypothyroidism

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Materials and methods
157 patients (118 women and 39 men) aged from 30 to 73 years with radical treatment for Graves' disease were included in this study. The patients were

divided into two groups depending: (76) included patients with low-normal level of TSH (0.4–2.0 mU/ml), the second group (81 patients) with upper-normal level of TSH 2.1–4.0 mU/ml. Quality of life was assessed with the help of the questionnaire Short-Form SF-36.
Results
In the first group the median follow- up after treatment 7 years (min 7; max 10), the median activity 9.7 mKu (min 4.0; max 18.6) the average level of TSH 1.07 mU/ml (0.4–1.37), a median dose of L-T_4 75 μg (min 50; max 100).
In the second group, the median follow-up after treatment of 8 years (min 7; max 10), the median activity 6.0 mKu (min 1.1; max 18.9), the average level of TSH 2.89 mU/ml (2.59–3.74), a median dose of L-T_4 75 μg (min 50; max 100).
In the evaluation of mean values of the quality of life in the first and second group, statistically significant differences were observed in the two indicators: physical functioning and general health were higher in group 1 ($P=0.01$ and 0.05), all other indicators on eight scales questionnaires were at a level above the average and between the groups did not differ.
Conclusions
The average quality of life of patients were on average and high level, however, there are significant differences in the quality of life among patients with upper- and low-normal TSH. It is established that patients with upper-normal TSH had the worst performance, in the course of our study revealed a statistically significant difference between multiple scales, such as physical functioning, the general state of health.

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P1044

ThyPROpl: the polish version of the thyroid-specific quality of life questionnaire ThyPRO

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Introduction
Thyroid disorders have significant impact on patients' quality of life (QoL). ThyPRO is a thyroid-specific QoL questionnaire applicable to patients with benign thyroid disorders. There is substantial evidence for its clinical validity and reliability in patients with benign thyroid disorders. ThyPRO consists of 85 questions summarized in 13 scales, measuring aspects of QoL relevant to thyroid patients. Our aim was to develop a validated Polish version of this questionnaire (ThyPROpl).
Methods
ThyPROpl was translated and validated according to standard methodology for translation of patient-reported outcomes (PRO). Firstly, two independent translations from English to Polish were performed by two translators native in Polish and a consensus version was reached, in collaboration with an in-country consultant. A third translator prepared a back–translation from Polish to English, which likewise was reviewed by the in-country consultant. The backwards translation was compared to the original English version by a PRO translation expert native in English (Health Research Associates HRA). If some discrepancies were found, the translation steps were repeated for those portions. The back-translated version was also reviewed by the developer of ThyPRO, who provided additional revisions. Finally, ThyPROpl was tested among five patients with thyroid disorders with cognitive interview techniques and new changes and clarifications needed for its full understanding were made.
Results
There was one major disagreement between the two translators during the forward translation step. During HRA evaluation 36 revisions were made by the in-country consultant and eight comments were provided by the developer. Based on patients' comments, five revisions were performed and subsequently tested by the in-country consultant. After proof-reading by external consultant recruited by HRA and formatting, ThyPROpl was finally approved.
Conclusion
ThyPROpl is a validated version of original ThyPRO questionnaire. We recommend the ThyPROpl for the evaluation of QoL among Polish patients with benign thyroid disorders.

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P1045

Evaluation of risk of hypothyroidism in pregnant women with overweight and obesity

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Introduction
Thyroid dysfunction affect up to 5% of pregnant women and hypothyroidism complicates up to 3% of pregnancies, of which 0.3–0.5% is diagnosed as overt, 2.0–2.5% as subclinical hypothyroidism. Obesity in pregnant women may further contribute to the development of hypothyroidism and adversely affect the pregnancy. The aim of the study was to assess the risk of hypothyroidism in overweight and obese pregnant women on the basis of concentrations of TSH, free T_3, free T_4, and thyroid peroxidase antibodies (aTPO).
Methods
The study included 16 overweight/obese (BMI 25.2–34.9 kg/m^2) pregnant women aged 22–41 years, patients of Gynecological Outpatient Clinic of the University Hospital. The control group consisted of 22 non-obese pregnant women with BMI in the normal range. In all subjects, serum concentrations of TSH, fT_4, fT_3 were determined twice during pregnancy and aTPO were measured in the first trimester.
Results
During the first trimester, median TSH concentration was higher 1.06 (0.47–2.38) mIU/l in overweight/obese than in non-obese women 0.65 (0.24–0.92) mIU/l ($P<0.05$). Median fT_3 and fT_4 did not differ significantly between both groups. aTPO concentrations were significantly increased in overweight/obese women (146.7 vs 32.8 IU/ml; $P<0.05$). At the second trimester, median TSH concentration was twofold higher in overweight/obese women compared to non-obese (1.63 vs 0.8 mIU/l; $P<0.05$); fT_3 and fT_4 did not differ significantly. Importantly, in overweight and obese women a more frequent incidence of pregnancy complications was observed. The percentage of pregnant women who developed hypothyroidism and were treated with L-thyroxine was higher in the study group compared to the control group.
Conclusion
Obesity is not uncommon in pregnant women and may increase the risk of hypothyroidism. It is important for doctors providing obstetric care to have wide understanding of the spectrum of thyroid disease occurring in pregnancy.

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P1046

Amiodarone induced thyrotoxicosis, a difficult cases report

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Introduction
There are two clinical types of amiodarone induced thyrotoxicosis (AIT). Type I AIT appears with hyperthyroidism and type II with a destructive thyrotoxicosis. Treatment of type I AIT includes antithyroid drugs meanwhile type II needs steroids as the first line therapy. If there is no respond to medical treatment, surgical approach must be considered. Here in we present a type II AIT case who had no respond to combined therapy therefore treated with surgical approach.
Case report
A 24-year-old female who had history of recurrent ventricular fibrillation, cardiomyopathy, and using 200 mg/day amiodarone per oral since 2 years. She was referred to our clinic as the thyroid function tests revealed thyrotoxicosis. She had no history of any thyroid disease. On physical examination thyroid gland was non palpable and there were no signs of thyroid ophthalmopathy. Thyroglobulin level was 317.4 ng/dl (1.4–78) and thyroid antibodies were negative. Doppler ultrasonography demonstrated a reduced vascularization in thyroid gland. Tc-99m sestaMIBI scan was not visualized the thyroid gland. The steroid therapy was started after discontinuation of amiodarone. Three weeks later methimazole and 4 weeks thereafter lithium were started because of the progression in clinical and laboratory findings. Despite current medical therapies, no improvement was

detected. Surgical approach was decided. Following of 12 sessions plasmapheresis, fT_3: 5.38 pg/ml (2.0–4.4) and fT_4: 3.25 ng/dl (0.93–1.7) levels were reduced. Subsequently, total thyroidectomy was performed without perioperative complications. Levothyroxine replacement was started and tapering of steroid therapy was planned. Patient was discharged from hospital by the third day.

Discussion

After the classification of AIT, the appropriate treatment must be started immediately due to high cardiac risk in these patients. Distinguish between two types of AIT is often difficult and usually combined therapy should be started. Persistent treatment choices must be considered in case of refractory to medical treatment.

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P1047

Study of thyroid function during pregnancy in a random population of Northern Greece

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It is well established that overt maternal hypothyroidism and subclinical hypothyroidism may be associated with an adverse outcomes for both the mother and offspring. Therefore, maternal hypothyroidism should be early diagnosed and treated.

Aim

The present study was designed in order to investigate thyroid function in the three trimesters of pregnancy, according to the recently updated guidelines.

Materials and methods

One hundred and fifty one ($n=151$) pregnant women, examined earlier than the 13th week of pregnancy for the first time in the Obstetrics Outpatient Clinic, were included in the study. Pregnant women were followed throughout pregnancy and assessments of TSH, FT_4, thyroid antibodies (antiTg and antiTPO) serum levels were carried out at first visit, in the second trimester (13–28 weeks) and in the third trimester (>28th week) of pregnancy. Level of statistical significance was set at $P<0.05$.

Results

In the first trimester, 20 (13.2%) pregnant women had TSH >2.5 μIU/ml, 20 (13.9%) had FT_4 <0.84 ng/dl and 19 (12.6%) had antiTg and/or antiTPO serum levels above normal. Subclinical hypothyroidism (TSH$>$ 2.5 μIU/ml ($n=20$) and normal FT_4 levels) was identified in 14 out of 20 women. Related samples Friedman's two-way ANOVA revealed that there was a significant increase of mean TSH levels between first and second trimester but non-significant between second and third trimester. Similarly, mean FT_4, antiTg and antiTPO levels were decreased significantly between first and second, but non-significantly between second and third trimester.

Conclusions

Given the fact that pregnant women with TSH >2.5 μIU/ml in the first trimester should receive thyroxine to avoid possible complications, and the fact that above 10% of pregnant women of our study had increased TSH levels, most of which had subclinical hypothyroidism, screening for TSH, FT_4 and thyroid antibodies is recommended in the beginning of pregnancy.

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P1048

Adherence of levothyroxine treatment in primary hypothyroid patients in Turkey: a multicenter study

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Non adherence to medication schedules by patients with chronic illnesses has long been recognized as a problem. The aim of this study is to evaluate levothyroxine (L-T_4) compliance, daily dosage and TSH levels under treatment in primary hypothyroid patients.

We included 1636 primary hypothyroid patients over 1 year under L-T_4 (F/M: 1469/167, 46 ± 13 years of age) included from 11 tertiary health care centres around Turkey. A survey covers on disease duration, daily dosage, adherence to L-T_4 recommendations were performed.

Duration of the L-T_4 treatment was 5.9 ± 6.7 years, L-T4 dosage was 96.6 μg/day and 1.3 μg/kg per day, TSH level was 4.8 mIU/l 32.3% of patients were not compliant to the treatment. Compliance rates differs between the centres with a maximum 84% and minimum 55%.

Noncompliant patients have higher TSH (6.9 ± 16 vs 3.8 ± 0.9 mIU/l, $P=0.01$) and shorter duration of disease (5.8 ± 6.9 vs 6.0 ± 6.5 years, $P<0.05$) compared to compliant patients. There was no difference of, dosage of L-T_4 between compliant and non-compliant patients.

Our results suggest that non-compliance of L-T_4 treatment is associated with subclinical hypothyroidism in our study group. Approximately 67.7% of patients follow treatment recommendations but compliance rates differs between the centre's. The physician–patient relationship seems to have key role in adherence to levothyroxine regimen.

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P1049

Thyroid hormone concentration and ultrasonographic findings in middle-aged lithuanian males and females from general population

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Introduction

Thyroid disorders are the most frequently diagnosed endocrinopathies prevalence of which is highly dependent on geographic region and age of study population.

Main objective

Evaluation of thyroid function and thyroid ultrasonographic features in 48–50-year-old people from general population in Lithuania.

Methods

During a 1 year period 395 randomly selected 48–50-year-aged men (169) and women (226) were enrolled into the study. Conventional thyroid ultrasound was performed and blood samples for hormone analysis were collected. TSH was analyzed using immunoradiometric method, FT_4 and anti-TPO – RIA (reagent kits of 'IZOTOP' Hungary).

Results

Mean thyroid volume of males and females was 16.9 ± 6.7 and 12.5 ± 5.3 ml respectively. Thyroid volume was larger ($P<0.001$) in men. 9.5% ($n=16$) males and 15.5% ($n=35$) females had enlarged thyroid gland, enlargement was more common in females ($P<0.01$). Thyroid hypoechoic echotexture was more common in females (51.8%, $n=117$ vs 26%, $n=44$), $P<0.001$. Thyroid nodes were detected in 37.2% ($n=84$) of females and in 24.9% ($n=42$) of males, overall in 31.9% ($n=126$) of study subjects. Thyroid nodes were more frequently diagnosed in females ($P<0.001$) than in males. Mean hormone levels were: TSH 1.65 ± 1.6 mU/l and FT_4 14.64 ± 2.63 pmol/l. Mean anti-TPO antibodies (TPOAb) in the study group was 52.86 ± 179.5 kU/l. Fifty-three study participants (13.4%) had positive anti-TPO. Sixteen (4.1%) individuals had elevated TSH (TSH >3.75 mU/l), in 5 (1.3%) individuals TSH was suppressed (TSH <0.27 mU/l).

Conclusions

i) Our findings that enlarged thyroid, hypoechoic thyroid, and multinodular goiter is more common in females than in males correspond to thyroid investigation results in other similar studies. ii) Prevalence of thyroid nodes (31.9%) seems to be slightly higher than in other populations. One possible explanation is that a universal salt iodization program in Lithuania has been introduced only recently.

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P1050

Selective embolization thyroid artery as a treatment for Graves' disease

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Background
Minimally invasive surgery in short time has been widely used in many fields of medicine and endocrinology not an exception. Having a number of advantages, such as small traumatic intervention, as well as cosmetic effect.
Materials and methods
Selective embolization thyroid artery (SETA), we used as an independent method of treatment Graves' disease (GD). Following this procedure the treatment of 17 patients received for the period from 2012 to 2013 years. Indications for SETA were: GD with severe concomitant diseases. Complicated forms of GD with decompensation. If the patient's categorical refusal from traditional operations for cosmetic reasons. Among the 17 patients had 2 (14.3%) men and 15 (85.7%) of women aged 22–56 years.
Results
Serious complications after SETA were noted in six patients had severe pain on the front of the neck, parotid region, lower jaw, headaches, which were stopped analgesics, pain duration of 3–4 days. In three cases after embolization were thyroiditis, manifests itself intoxication syndrome, which was cupping antibacterial therapy. In the study of the hormonal status on the 5th day a marked increase in the level of hormones. When monitoring the Doppler ultrasound scan of the thyroid gland 7th day revealed the absence of blood flow in the gland, and thyroid volume reduction of 30–35%. On the 7th day after the REE held needle aspiration biopsy of thyroid. At the same time identified changes, such as acute infarct and necrosis glandular epithelium and interstitium fibrosis gland tissue. On the 30th day after embolization, downward trend in the levels of the hormone.
Conclusion
SETA is contemporary minimally invasive treatment that requires further study. Its use is possible in severe forms of GD and the presence of severe concomitant diseases. The method facilitates fast enough cupping effects of hyperthyroidism, thyroid volume reduction.

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P1051

Postoperative monitoring and replacement therapy after resection of the thyroid gland

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Introduction
The problem of postoperative hypothyroidism has the same long history as thyroid surgery. Levothyroxine monotherapy is the treatment of choice for hypothyroid patients because peripheral T_4 to T_3 conversion is supposed to account for the overall tissue requirement for thyroid hormones.
The aim of this retrospective study conducted in the hospital is to evaluate the effectiveness of levothyroxine monotherapy in patients undergoing thyroidectomy.
Materials and methods
The study included 42 patients after thyroidectomy with normal levels of TSH (1–3 mU/l) on the background of levothyroxine monotherapy (all of them were treated with 1.5 mg/kg per day dosage for at least 2 months); and 85 of them, with euthyroid, belonged to a control group. The determining of TSH, FT_4 and FT_3 in serum by immunochemical analysis has been conducted through 2 weeks, 1–2–6–12 months after surgery.
Results
The research revealed that while prescribing levothyroxine, the increase in the concentration of FT_3 in the blood is slow and is reaches the desired parameter for full compensation of hypothyroidism only after 1–2 months. However, about 20% of levothyroxine-treated athyreotic patients FT_4 levels were 5.6% higher and FT_3 levels were 12% lower compared to the control group.
Conclusion
Therefore, levothyroxine monotherapy is effective compensation in most postoperative hypothyroid patients, but some of them need a more personal approach to replacement therapy, which can be achieved by means of postoperative monitoring.

Keywords
postoperative monitoring, replacement therapy, levothyroxine monotherapy.
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P1052

Prevalence of thyroid dysfunction and thyroid auto-antibodies among persian pregnant women

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Introduction
Maternal thyroid deficiency can induce serious adverse events on both mother and fetus during the whole period of pregnancy. The purpose of this study was to determine various epidemiological aspects of thyroid dysfunction among persian pregnant women.
Methods
Four hundred-eighty pregnant women with a mean age of 26.9 ± 5 regardless of their gestational age were registered. After recording their medical history, serum samples were collected to measure thyrotropin (TSH), free thyroxine (FT_4) and thyroid auto-antibodies (anti-TPO and anti-Tg). Thyroid dysfunction was defined by the trimester-specific reference intervals for TSH and FT_4.
Results
The prevalence of elevated and depressed TSH for gestational age was 19.4 and 1% respectively. Overall anti-TPO antibody were detected in 31 (6.4%) women, and 12 (12.8%) women with high TSH were anti-TPO positive. Subclinical hypothyroidism was observed in 82 (17.1%) during all trimester while the prevalence of overt hypothyroidism and isolated hypothyroxinemia were 2.5 and 8.7% respectively. The prevalence of subclinical hypothyroidism in the first, second and third trimesters were 13.4, 20.7 and 65.8% respectively. Regarding thyroid auto-antibodies 12 (14.4%) women with subclinical hypothyroidism were ATPO positive while 7 (8.4%) of them had both ATPO and TG antibody positive.
Conclusion
The Persian pregnant women studied here, had much higher prevalence of subclinical hypothyroidism and overt hypothyroidism compared to western population (17 vs 2.5–6% and 2.5 vs 0.5% respectively). The causes for the higher prevalence estimates should be investigated and clarified.

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P1053

Thyroid volume in adult β-thalassemic patients is smaller than in controls

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Introduction
Thyroid function is commonly impaired in β-thalassemic patients with an estimated prevalence of hypothyroidism of 9–11%. According to literature, iron overload is the main cause of tissue damage involving both thyroid and pituitary gland, thus leading to primary or secondary hypothyroidism respectively. However, thyroid morphology has been rarely investigated in adults. The aim of this study is to evaluate thyroid volume (TV) and thyroid morphology in β-thalassemic adult patients compared to healthy controls.
Methods
We performed a cross-sectional, controlled study in 13 β-thalassemic adult patients (six males and seven females) (36.36 ± 4.26 years) and 120 healthy volunteers (28 males and, 92 females) (38.1 ± 4.9 years). All subjects underwent thyroid ultrasonography performed by the same operator. TV was calculated as the sum of the volume of the two lobes, each estimated by standardized formula: length × width × depth × 0.479. Ultrasound evaluation included the presence/absence of hypoechogenicity and echotexture heterogeneity, and the presence/absence of nodules.
Results
TV was significantly lower in β-thalassemic patients (5.41 ± 1.33 ml) than in the control group (8.45 ± 2.81 ml) ($P < 0.001$) independently from their thyroid function (euthyroidism or hypothyroidism). The prevalence of diffuse echotexture heterogeneity and hypoechogenicity of the thyroid was significantly higher in thalassemic patients (92.3%) than in the control group (42.4%) ($P < 0.001$). Thyroid antibodies were negative in all thalassemic patients. Thyroid nodules were found in four thalassemic patients (30.7%) and in 44 volunteers (36.7%) ($P = 0.674$).
Discussion
In adult β-thalassemic patients TV was smaller than in healthy subjects even when patients with a normal thyroid function were considered. Moreover the prevalence of hypoechogenicity and echotexture heterogeneity, without a confirmed diagnosis of autoimmune thyroiditis, was higher. These results suggest a primary thyroid damage, characterized by thyroid hypoplasia and tissue alterations probably caused by iron infiltrates. Furthermore, the risk of developing thyroid nodules seems not to be increased in beta-thalassemic patients.

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P1054

Steroid treatment in patients with active moderate-to-severe Graves orbitopathy

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Background
Although IV steroids are the treatment of choice for moderate-to-severe graves orbitopathy (M-S GO), the most efficacious regimen is not yet defined. Cases not responding or relapsing after steroid treatment (STx) are not uncommon and STx can cause serious adverse events. The aim of the present study is to define the steroid regimen which balances between efficacy and damage, using stir-sequence orbital-MRI (SsMRIo) as an additional objective tool for the evaluation of activity and severity of GO.
Methods
Forty-seven patients with M-S GO received a cumulative dose of 4.5 g of methylprednisolone in 12 weekly doses. Two weeks post iv-STx, peros-STx (prednisolone for 3 months) was administered to patients with clinical and MRI findings of active disease. CAS and TES scores were measured at baseline, 6, 12 and 24 weeks and SsMRIo was performed at baseline and 12 weeks. Quality of life was evaluated (GO-QoL questionnaire) at baseline, 12 and 24 weeks.
Results
Age was 58.46 ± 13.37 (mean ± s.d.), 70.2% were females and 37.8% current smokers. Duration of ocular symptoms was 12.22 ± 13.23 months. Owing to adverse events 10.6%(5/47) discontinued iv-STx. Peros-STX following the IV received 52.4% (22/42) based on the SsMRIo. At the end of the treatment significantly better CAS (CAS at baseline: 6.06 ± 1.17 and at 24 weeks:1.28 ± 1.55, $P < 0.001$) and TES scores (TES at baseline:18.33 ± 6.63 and at 24 weeks: 8.68 ± 7.24, $P < 0.001$) were observed. QoL significantly improved in all domains (Social function at baseline: 3.77 ± 2.79 and at 24 weeks: 7.45 ± 2.98, $P = 0.000$, dependency at baseline: 5.45 ± 3.21, at 24 weeks: 9.05 ± 2.19, $P = 0.000$). Recurrence was comparable in the groups (2/22 and 2/20 patients after having and not having received peros-STx).
Conclusions
Combination of iv-STX and peros-STx is an efficacious and safe regimen for the treatment of GO. SsMRIo can improve the detection of those cases which remain active and need further peros-STx after the iv-STX.

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P1055

The influence of radioiodine therapy in 1600 patients with subclinical hyperthyroidism

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The aim of our study was to assess the influence of radioiodine (^{131}I) therapy on the achievement of euthyroidism, prevention of adverse effects on the cardiovascular and prevent evolvement to overt hyperthyroidism.
Materials and methods
We treated 1600 patients refered to our department during the last 8 years, aged 23–77 years; 89% of them were females and 11% males; 520 patients with multinodular goitre (MNG), and 1080 patients with autonomous nodule (ATN). Some of the patients were treated with antithyroid drugs for 1–3 months before ^{131}I therapy (148 patients). Malignant changes were excluded in all nodules by fine-needle aspiration biopsy. All the patients had serum TSH levels < 0.1 mU/l and effective T-half was more than 3 days at the time of treatment. The activity dose was calculated by the use of Marinelli's formula and ranged between 200 and 800 MBq. The absorbed dose (Gy) ranged between 180 and 300, and was proportional to thyroid volume. Follow-up control was done every 6 weeks.
Results
Euthyroidism achieved in 99% of patient with ATN and 93% of MNG; 1% of patients with ATN and 6% of patients with MNG develop hypothyroidism. One percentage of patients with MNG were in subclinical hyperthyroidism and received second dose of radioiodine therapy. In all of the patients, the symptoms and signs of subclinical hyperthyroidism disappeared (palpitation, tachycardia, atrial fibrillation, exercise tolerance improved, the blood pressure normalised and the quality of life improved).
Conclusions
The achievement of euthyroidism and the remission of the symptoms and signs of subclinical hyperthyroidism, were due to good diagnosis, well preparation of the patients; accurate measurement of administered activity, effective half-life, and well-organised follow-up. We recommend early treatment of subclinical hyperthyroidism, and long period of follow-up to evaluate the long-term effect of radioiodine therapy.
Subclinical hyperthyroidism, and long period of follow-up to evaluate the long-term effect of radioiodine therapy.

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P1056

Hydrolytical activity of autoantibodies to double-stranded DNA in autoimmune thyroiditis

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Objective
To evaluate the hydrolytical activity of autoantibodies (Ab) to double-stranded DNA using atomic force microscopy in patients with autoimmune thyroiditis.
Methods
Ab to double-stranded DNA (dsDNA) IgG class were isolated from the serum of patients with autoimmune thyroiditis by DNA-affinity chromatography. Hydrolytical activity of Ab to dsDNA was confirmed by Polyacrylamide Gel Electrophoresi (PAGE). The images of Ab to dsDNA and results of dsDNA's hydrolysis were recorded by atomic force microscopy (AFM). Two kinds of substrate were used: plasmid DNA PBr –322 for PAGE and chickens erythrocytes chromosomal DNA for AFM.
Results
Usage of AFM allowed to get images of chromosomal DNA from chicken erythrocytes and Ab to dsDNA from patients with autoimmune thyroiditis and to measure molecular's size and weight. Ab to dsDNA and chromosomal DNA interaction leads to appearance of DNA fragments with low molecular weight via to control samples. This effect explains by hydrolysis of DNA molecule. The number of short DNA fragments directly depends on the length of the reaction. An interaction area between Ab to dsDNA and chromosomal DNA has more large size than the free DNA molecule: diameter – 11.4–39.7 nm and height – 0.47–1.9 nm. Newfound Ab- DNA complexes are highly stable: hydrolysis of phosphodiester bonds of DNA molecule did not results in Ab release. This indicates that investigated Ab has nonprocessive action's mechanism.
Conclusion
Our study demonstrates the presence of hydrolytical activity against dsDNA in Ab isolated from serum of patients with autoimmune thyroiditis and highlights an affective role of Ab to dsDNA in pathogenesis of Hashimoto's thyroiditis.

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P1057

Analysis of chosen polymorphisms in *FoxP3* gene in children and adolescents with autoimmune thyroid diseases

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Forkhead box P3 (Foxp3) is an important regulatory factor for the development and function of T regulatory cells (Tregs). Moreover it has been established that deficiency of the *Foxp3* gene in Treg cells suppresses their regulatory function leading to the development of autoimmune thyroid diseases (AITDs). The aim of our study was to estimate the association of three polymorphism of *FOXP3* gene with the predisposition to GD and HT in children.
The study was performed in the group of 145 patients with GD (mean age, 16.5 ± 2), 87 patients with HT (mean age, 15.2 ± 2.2) and 161 healthy volunteers (mean age, 16.3 ± 3). DNA was extracted from the peripheral blood leukocytes using a classical salting out method. The three SNPs rs3761549 (−2383C/T), rs3761548 (−3279G/T) and rs3761547 (−3499T/C) in the *FOXP3* gene were genotyped by TaqMan SNP genotyping assay using the real-time PCR method.
In our study, rs3761549G/A genotype was more frequent in females with GD in comparison to healthy female subjects (15 vs 7%, $P = 0.033$) with OR = 2.15 and 95% CI for OR: 1.07–4.63. We also observed rs3761547T/C to be more frequent in females with GD in comparison to control females and this difference was close to being statistically important (13 vs 7%, $P = 0.066$) with OR = 1.99 and 95% CI for OR: 0.96–4.48. There were no significant differences in males in the analyzed SNPs and in females with rs3761548 SNP.
In conclusion, these results may suggest that rs3761549G/A polymorphism in *Foxp3* gene could contribute to GD development in females.

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P1058

The clinical values of IGF1 and IGF-binding protein-3 levels in blood and thyroid nodules

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Introduction
Serum and intranodal levels of IGF1 and IGF-binding protein 3 levels (IGFBP3) were determined in patients with nodular thyroid diseases.
Materials and methods
Demographic, clinicopathological and laboratorial caracteristics of the subjects were recorded. After performing fine needle aspiration biopsy, IGF1 and IGFBP3 levels were determined in blood and aspiration samples. Clinicopathological and laboratorial findings were analysed.
Results
The serum levels of IGF1 (232.8 ± 12.9 ng/ml) and IGFBP-3 (4.8 μg/ml (2.2–6.4)) were found significantly higher than intranodal (IGF1 39.1 ng/ml (32.6–49.8); IGFBP3 0.173 μg/ml (0.07–0.64)) levels ($P < 0{,}01$). A positively correlation between serum levels of IGF1 and intranodal levels of IGF1 were observed ($P < 0.01$, $r = 0.42$). Serum level of IGF1 of women patients were found significantly higher than men ($P = 0.028$). The ratio of differentiated thyroid cancer in all cases was 3.75%, and it was 23% in operated patients. Intranodal levels of IGF1 and IGFBP3 in subjects with multinodularities were higher than in cases with single nodules ($P = 0.043$). A positive correlation between the nodular sizes and the serum levels of IGFBP3 was detected ($P = 0.042$, $r = 0.23$).
Conclusions
The pathogenetic clues of thyroid nodules include the increased sizes and multinodulations of the thyroid nodules in this study. These data indicate that both IGF1 and IGFBP3 play an important role in the mitogenic signalling in thyroid nodules.

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P1059

Voluntary supplementation does not fully correct iodine deficiency among Latvian pregnant women: a national cross-sectional survey

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Introduction
Low iodine intake during pregnancy may cause thyroid dysfunction, which might result in an inadequate foetal brain development. Although Latvia has been considered iodine replete, newborn TSH screening data suggest some iodine deficiency. In the absence of universal salt iodization programme we conducted a nation-wide study of pregnant women from all regions of Latvia.

Methods
The study enrolled 426 pregnant women. They were asked to fill a questionnaire on dietary habits concerning iodine intake ($n=405$). Thyroid function (TSH and FT4) and antibodies (-TPO-Ab) were measured ($n=288$). Urinary iodine was measured with ammonium persulfate method ($n=380$).
Results
The median creatinine-standardized urinary iodine concentration (UIC) was 81.6 (IQR 46.5–130.7) μg/g Cr during pregnancy (68.40 (IQR = 53.46–91.09) μg/l). 81.8% of pregnant women had the UIC under the WHO recommended range of 150–250 μg/g. The median UIC was the lowest during the first trimester of pregnancy (68.6 (IQR = 37.0–113.2) μg/g Cr), reaching higher concentrations in the second and third trimester: 87.3 (IQR = 47.4–130.2) and 87.2 (IQR = 53.0–145.5) μg/g Cr respectively. Women reporting regular iodine supplementation in the form of iodized salt or seafood consumption had higher median UIC (65.9 (IQR = 39.8–102.2) vs 86.3 (IQR = 49.0–140.1) μg/g Cr respectively) than those with no supplementation (29.6% of respondents; $P=0.004$). The self-reported prevalence of iodized salt consumption was 52.1% and it was associated with higher median UIC (85.7 vs 79.7 μg/g Cr) without statistical significance ($P=0.18$). Women taking iodine supplements (16.4% of respondents) had higher median UIC than those without supplementation: 92.4 (IQR = 48.5–164.6) vs 80.4 (IQR = 46.2–124.9) μg/g Cr respectively, not reaching statistical significance ($P=0.16$). The median anti-TPO antibody concentration appeared to be lower in women taking iodine containing supplements ($P=0.047$).
Conclusion
The median UIC indicates iodine deficiency in pregnant women in Latvia. Correction of iodine deficiency with 150 μg iodine daily should be considered for recommendation.

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P1060

THRB expression is affected by miR-26a and miR-496, but age-associated decrease of the expression of this gene in human peripheral blood mononuclear cells is not dependent on these miRNAs

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Introduction
Decreased function of the thyroid axis during aging is associated with a better functional performance and longer survival. This phenomenon can be a result not only of a lower production of thyroid hormones including bioavailable triiodothyronine, but also of age-associated alterations regarding triiodothyronine receptors.
Methods
Functional studies regarding interaction between the 3′UTR of TRβ1 mRNA and *in silico*-identified miRNAs (miR-26a and miR-496) that potentially interact with this mRNA, were performed in HEK293 cells. Analysis of the expression of *THRB* and abovementioned miRNAs was performed in peripheral blood mononuclear cells (PBMCs) of young (Y, $n=53$, 18–42 years), elderly (E, $n=50$, 60–75 years), and long-lived (L, $n=51$, >90 years) individuals using Q8 real-time PCR. Statistical analysis was performed using Student's *t*-test, Kruskal–Wallis test, and Spearman's rank correlation coefficient.
Results
Functional studies showed that miR-26a interacted with two sites located within the 3′UTR of TRβ1 mRNA and that such interaction resulted in the reduction of activity of the reporter protein by 31 and 23.5%, ($P<0.0001$ and $P=0.0005$ respectively). miR-496 interacted with one of the two putative binding sites within the tested 3′UTR and reduced the activity of the reporter protein by 42.3% ($P<0.0001$).The median expression of *THRB* was significantly lower in the long-lived than in young group ($P=0.03$). In addition, the median expression of miR-26a was also significantly lower in the long-lived than in young group ($P=0.032$), while the expression of miR-496 was not affected by age in PBMCs. There was no correlation between the expression of *THRB* and of both miRNAs.
Conclusion
Age-related decrease of the expression of *THRB* in human PBMCs is independent of both miR-26a and miR-496.

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P1061

Hyperthyroidism during pregnancy: the role of measuring maternal TSH receptor antibodies and fetal ultrasound monitoring

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Aim
To evaluate the usefulness of measuring maternal anti-TSH receptor antibodies (TRAbs) and fetal ultrasound (US) monitoring in cases of current or past maternal hyperthyroidism.
Materials and methods
A 77 pregnant women with active hyperthyroidism irrespective of its cause or with history of Graves' hyperthyroidism were observed prospectively. Maternal serum TSH, fT_4, fT_3, TRAbs, and fetal US were performed at baseline and repeated every 2–4 weeks when needed. Neonatal thyroid status was assessed based on serum TSH, fT_4, and fT_3 obtained in the first days of life.
Results
A 35 women were diagnosed with gestational hyperthyroidism and 42 with Graves' disease; among them 26 had current and 16 past hyperthyroidism. Fetal and neonatal thyroid dysfunction occurred only in cases of maternal Graves' disease: 9 (21%) and 3 (7%) respectively. Active maternal Graves' hyperthyroidism and TRAbs elevated at least five times above the upper normal limit predisposed to fetal hyperthyroidism. Maternal anti-thyroid drug therapy, and low TRAbs and fT_4 were the risk factors of fetal hypothyroidism. Abnormal fetal thyroid sonogram was the only indication of fetal thyroid dysfunction. Increased blood flow throughout the whole thyroid gland (central hypervascularization), hypoechogenicity, goiter or thyroid size in the upper normal range were fetal signs characteristic for hyperthyroidism. Goiter without increased vascularization or with increased peripheral blood flow represented fetal sign of hypothyroidism. Four patients had high TRAbs in the third trimester (10.8–29.9 IU/ml), but neither fetal nor neonatal thyroid dysfunctions were noted.
Conclusions
In the cases of maternal Graves' disease, fetal thyroid dysfunction occurs more often than commonly assumed. Fetal thyroid US is a valuable tool in early diagnosing and monitoring of the fetal thyroid status in pregnancy complicated by maternal Graves' disease. The evaluation of biological activity of maternal TRAbs may be helpful in prenatal diagnosis in some cases.

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P1062

High mean platelet volume in hyperthyroid patients after radioactive ^{131}I treatment

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Introduction and objective
Recently, a lot of studies associated with high mean platelet level (MPV) in patients with hypo- and hyperthyroidism has reported in medical litherature. But it is not clear whether or not radioactive iodine treatment effect on platelet activity. It is well known that elevated platelet size is associated with its high enzymatic and metabolic activity. Aim of our preliminary study is to determine the platelet size via MPV level in hyperthyroid patients undergoing radioactive iodine ablation treatment.
Patıents and methods
Thirty-four patients with hyperthyroidism treated with a therapeutic dose of ^{131}I in our endocrinology department between 2009 and 2013 years were included this retrospective study. Patients treated with radioiodine received a single therapeutic dose of ^{131}I (range 8–15 μCi). Free T_3, free T_4 and TSH levels were performed before and after the RAI ablation treatment. All these parameters were reevaluated at least after 1 year from RAI ablation treatment. All hormonal analyses were performed by chemiluminescence assay. Complete blood count analysis was measured by the automatic hematology analyzer Beckman Coulter LH 750. BMI was calculated by using a formula as weight (kg)/(height (m))^2.

Results
The mean age in present study population was 42.1±8.4 yeara. In demographic features of patients, mean BMI was 25.8±2.7 kg/m^2, mean waist circumference was 91.0±9.0 cm. Before RAI treatment the mean free T_3 levels was 4.5±1.6 pg/ml; the mean free T_4 levels was 1.4±0.6 ng/dl; the mean TSH levels was 0.06±0.08 μIU/ml; after RAI treatment, the mean free T_3 levels was 3.07±0.5 pg/ml; the mean free T_4 levels was 1.1±0.2 ng/dl; the mean TSH levels was 1.6±1.3 μIU/ml. The mean MPV levels before the treatment (8.5±1.2 fl) was found increase when compare with (8.0±1.2 fL) ($P=0.0001$) after the treatment.
Conclucion
Our present study indicated that MPV is a decrease after RAI ablation treatment. A previously study has reported that after 3 weeks of antithyroid drug therapy there was a significant decrease in MPV compared with the pretreatment values in hyperthyroid patients. Our preliminary study is the first notice that RAI therapy may have beneficial effect on MPV levels. Further studies are needed to explain this subject.

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P1063

Inferior oblique muscle enlargement in a patient with Grave's orbitopathy

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Graves' orbitopathy (GO) is an auto-immune disorder that targets intra-orbital tissues. It is well proven to involve inflammatory hypertrophy of the rectus EOMs. Superior oblique (SO) muscle has been sporadically reported to be involved in GO. However, there are extremely few reports in the literature that refer to the involvement of the inferior oblique (IO) muscle and here we present such a case. A 33-year-old man with unilateral exophthalmos was referred to our clinic. Mild swelling of both eyelids was present, along with mild eyelid redness, chemosis and redness of the conjunctiva and swelling of the caruncle and plica, in both eyes. Sign of attentive gaze and upper eyelid retraction were observed, notably at the left, so that the left eye manifested a 3 mm distance of upper eyelid from the upper limbus. Palpebral aperture was assessed (right eye was measured 11 mm and left eye 14 mm). The patient suffered of double vision at all gaze positions, being more severe at upgaze, with moderate motility, mainly of the left eye, on up-gaze. Hertel evaluation revealed exophthalmos of the left eye. Clinically and biochemically he was hyperthyroid, with positive TRAbs. A STIR magnetic resonance imaging of the orbits showed minimal active inflammation and enlargement of all four rectus extra-ocular muscles (EOMs), bilaterally, with a very impressive enlargement of the inferior oblique muscles in both eyes. The patient was diagnosed with GO and received i.v. steroid treatment (i.v.-STx) of 12 weekly doses (cumulative dose 4. 5 g methylprednisolone). A significant clinical and imaging improvement was observed at the end of the i.v.-STx. Repeated MRI showed significant reduction of the dimensions of the EOMs, with the inferior oblique returning back to almost normal size.
Thus inferior oblique enlargement, although rare, can also be involved in patients with GO.

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P1064

Solitary autonomously functioning thyroid nodule and severe osteoporosis

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Objective
Thyrotoxicosis have received wide attention from researchers over the last century as it an important cause of secondary osteoporosis. Most of the cases present mild osteoporosis.
Design
We present the case of a old women (77 years) with no thyroid disease in medical history, only with stable hypertension and artrosis. She was sent to endocrine exam by the oncologyst because she started to have intense lumbal painand the MRI describe osteolitical areas in Th12 and L2, L3. Achieving positron emission tomography–computed tomography (PET–CT) showed that the thoraco-lumbar spine lesions were not metastases only serious osteoporotic areas and also identified a nodule with high sensitivity to 18-FDG in right thyroid lobe 6 cm. The ultrasound demonstrate a hipoecoic nodule with intense vascularization about 6 cm, and radioioduptake showed an intense uptake in this nodule and TSH was 0.0003 μUI/ml. FNA was performed and the result excluded a malign lezion. We recommend thyroidectomy and the final hystopathologic exam was benign.
Results
The diagnose was toxic solitary autonomous thyroid nodule with severe osteoporosis wich mimicks bone metastasis at the begining.
Conclusion
Hyperthyroidism, even with mild simptoms may be a contributing factor to the development of osteoporosis in some post-menopausal women, mostly at lumbal sites. A solitary autonomously functioning thyroid nodule affects bone metabolism and is a risk factor for osteoporosis.

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P1065

Assessment of thyroid function and volume in hypogonadal patients

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Background
Hypogonadism is related to additional endocrine abnormalities. Thyroid abnormalities may be common in hypogonadism patients, although this association is not clear.
Objective
In this study, we examined the incidence of thyroid disorders in hypogonadisms.
Methods
A case–control study of 68 hypogonadal patients and 74 age-matched healthy controls from the general population was conducted. Thyroid function, thyroid volume measurements, and presence of thyroid autoantibodies were examined.
Results
The mean BMI and age of the patient and control groups were similar ($P=0.43$ and $P=0.407$ respectively). The thyroid status differed significantly between the patient and control groups ($P=0.002$). In the patient group, 55 (80%) patients were euthyroid, 10 (14%) patients were hypothyroid, and 3 (6%) patients were hyperthyroid. In the control group, 71 (95%) subjects were euthyroid, and 1 (5%) was hypothyroid. Serum TSH levels were significantly higher in hypogonadal patients than in controls ($P=0.018$); however, serum free T_4 and free T_3 levels did not differ significantly between the two groups ($P=0.29$ and $P=0.63$ respectively). The presence of thyroid autoantibodies (anti-TPO and anti-TG) did not differ significantly between the patient and control groups ($P=0.49$ and $P=0.89$ respectively). There were no differences observed by ultrasonography between the patient and control groups. The thyroid volumes of the right and left lobes were measured. There were no significant differences in thyroid volumes of the patient and control groups (59.67±30.34 and 68.02±43.45 ml respectively; $P=0.22$).
Conclusion
A high incidence of hyperthyroidism and a high incidence of hypothyroidism were observed in hypogonadal patients.

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P1066

MRI evaluation of extraocular muscles in patients with Grave's orbitopathy

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Background
Clinical evaluation of Graves' orbitopathy (GO) is often insufficient. Frequently it is difficult to decide whether a case of GO is active, or to detect the degree of severity. STIR sequence MRI suppresses signal from fat and thus in the orbits can also detect active inflammation and oedema of extra-ocular muscles (EOMs). The aim of the present study is to examine whether imaging of rectus EOMs with STIR MRI could provide additional information for the activity and severity of GO.
Materials and methods
A 3 Tesla STIR sequence MRI was used to measure maximum diameter of rectus EOMs in 72 healthy individuals (Group A), in 24 patients with Graves' disease without GO (Group B), and in 31 patients with moderate-to-severe GO (Group C). Additionally, the area of the EOMs was calculated: for superior and inferior rectus at the coronal plane, and at the axial plane for the medial and lateral rectus.
Results
Patients in group C had significantly larger all four EOMs, in both diameter and area, compared to group A. Also, in comparison with group B, patients in group C had significantly larger Medial, Superior and Inferior rectus, also in both diameter and area. Significantly larger, in both diameter and area, were found to be all the EOMs, except the Superior Rectus, in Group B compared to Group A. Multiple linear regression showed that age and sex did not influence dimensions of EOMs in the three groups.
Conclusions
In patients with GD orbital MRI can detect enlargement of the EOMs before expressing any ocular signs and symptoms. Orbital MRI can be used as an objective tool for the evaluation of activity and severity of GO.

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P1067

Successful preoperative treatment of toxic nodular goiter patient with agranulocytosis using plasmapheresis

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Agranulocytosis is an uncommon but very serious complication during treatment with thyrostatic. In case of severe hyperthyroidism removal of circulating thyroid hormones by plasmapheresis may be an effective therapeutic option.
We present the therapeutic difficulties and successful treatment with preoperative plasmapheresis in 63-year-old female patient with severe hyperthyroidism in the course of toxic nodular goiter and agranulocytosis, which occurred after 3 weeks of taking thiamazole. We modified and applied the treatment with propylthiouracil and lithium carbonate during hospitalization in the Department of Endocrinology. In consequence of using recombinant granulocyte–colony stimulating factor we achieved normalization of neutrophils in the blood. We have decided to thyroidectomy as a life-saving operation because of difficulties in obtaining euthyrosis during the current treatment. We gave organic iodine and conducted two plasmapheresis treatments to give a reduction in the concentration of free thyroid hormones. Plasmapheresis in the perioperative period may cause excessive bleeding during surgery. The potential deficiency of coagulation factors we completed using fresh frozen plasma (FFP). The patient underwent with no complications total thyroidectomy.

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P1068

The lipid profile in patients with subclinical hypothyroidism and metabolic syndrome

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Background
We know that lipid profile is disturbed in both subclinical hypothyroidism (SH) and metabolic syndrome (MetSy). In this study we observed lipid profile in newly diagnosed patients with SH and MetSy.
Materials and methods
We chose 70 patients (all females) with newly discovered SH and 20 healthy controls, mean age 51.1 ($\pm$6.79). The parameters that we determined are: TSH, FT_4, anti-TPO-At, triglycerides, whole, LDL and HDL cholesterol. For statistical calculations we used EXCEL, Med-Calc and SPSS Programs.
Results
The patients were additionally divided in two subgroups, considering existence of type 2 diabetes mellitus (DM), one with and the other without DM.The patients had higher levels of whole and LDL cholesterol than the control group ($P=0.02$). The levels of triglycerides had no difference between groups. The percentage of women with level of HDL cholesterol lower than 1.29 mmol/l is almost the same in the three groups ($P=0.953$). The percentage of women with level of triglycerides higher than 1.69 mmol/l is statistically significant between three groups ($P=0.01$). The highest percentage with high triglycerides is in the group of patients with SH and DM (66.7%), while the lowest is in the control group (20%). We didn't find correlation between TSH, FT_4 and antiTPO-At and levels of triglycerides and cholesterol.
Conclusion
Considering the results of this study we may conclude that the patients with SH and MetSy has a higher risk for developing of coronary disease and hypertension.

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P1069

Hypertensive patients with mild hypothyroidism show less frequent spontaneous normalization of thyroid function than normotensive patients

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Introduction
Overt hypothyroidism is associated with diastolic hypertension, but in subclinical hypothyroidism, data are inconclusive. HS tiroxina is a double-blind trial evaluating the effect of levothyroxine on blood pressure in patients with mild SH (TSH 5.0–9.9 mU/l and normal free T_4) and moderate-to-high cardiovascular risk.
Methods
We analized baseline data of the first 46 patients screened. Confirmatory thyroid function tests were repeated 2–4 weeks after initial diagnosis. Only patients with persistent SH were randomized. Measurements included 24 h-blood pressure monitoring, TPO antibodies, lipids and urinary sodium excretion. Patients were not taking drugs known to interfere with thyroid function tests. Factors associated with spontaneous TSH normalisation were assessed.
Results
Most patients were female (76.1%), their mean age was 59.83 (s.d. 7.18) years, BMI: 31.09 (5.39) kg/m^2, 67.4% had diabetes, 8.69% prediabetes (HbA1c $>$5.7%) 69.6% had dyslipidaemia, 8.7% smoked and 69.6% were hypertensive. In the confirmatory measurement, 19.6% showed normal thyroid function. This happened more frequently in normotensive patients (66.7 vs 21.6%, $P=0.015$). TSH was 6.6 (1.35) and 3.59 (0.7) mU/l in persistent SH and euthyroid subjects, respectively. No differences in anti-TPO antibody positivity, age, gender, urinary sodium excretion, prevalence of known dyslipidaemia or number of CVRF were found between patients who normalised TSH and those with persistent SH. However, differences were found in BMI (SH: 32.1(4.48) vs 26.17(7.0) kg/m^2, $P=0.015$) and in LDL (SH: 105.9 (37.25) vs euthyroid

141.26 (38.95) mg/dl, $P=0.015$) and total cholesterol (186.6 (41.7) vs 224.2 (41.2) mg/dl, $P=0.019$). In SH, TSH was positively correlated with mean nocturnal blood pressure ($r=0.49$, $P=0.017$) and tended to be correlated with diurnal blood pressure ($M=0.087$), too.
Conclusions
In our population, spontaneous normalisation of TSH in SH is less frequent than previously reported. Hypertensive patients have a higher risk of persistent SH and TSH is correlated with blood pressure.

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P1070

Ultrasound thyroid imaging, TSH and anti-thyroid peroxidase antibodies concentrations in Warsaw adolescents: the influence of family history of thyroid disease: preliminary results

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Introduction
Data regarding the thyroid gland evaluation in Polish adolescents are limited.
Aim
The aim of the study was to asses TSH and anti-thyroid peroxidase antibodies (anti-TPO) concentrations as well as thyroid morphology on ultrasound in Warsaw adolescents in regard of family history of thyroid disease.
Materials and methods
The study was carried out on a group of 480 adolescents (285 girls and 195 boys), aged 17–18 years, from two Warsaw high schools. All subjects were asked to answer questionnaire regarding family history of thyroid disease. We measured serum levels of TSH and anti-TPO and performed thyroid ultrasound.
Results
Positive family history of thyroid disease declared 43% of the subjects. The mean thyroid volume was 9.85 ml (4.54–24.69, S.D. $\pm$3.31) for females, and 13.31 ml (5.46–60.95, S.D. $\pm$6.89) for males and did not differ significantly between subjects with and without thyroid disease in family. In the group with positive family history of thyroid disease abnormal TSH concentration was found in 3.2%, elevated anti-TPO concentration in 6.4% and abnormal ultrasound thyroid image in 30% of subjects, while in the group with negative family history in 2.6, 2.6 and 14% respectively. The most common pathology in both groups was generalized thyroid hypoechogenicity (16.7 vs 12.7%). Thyroid nodules were found in 8.8 and 5.6% of patients respectively. Increased levels of TSH, anti-TPO, thyroid hypoechogenicity and focal lesions were significantly more common in girls than in boys in both groups. Abnormal ultrasound image was more sensitive indicator of hypothyroidism than elevated levels of anti-TPO antibodies.
Conclusions
The results indicate that thyroid pathology concerns about 1/3 of adolescents with positive family history of thyroid disease and is substantially less frequent in those without thyroid diseases in family.

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P1071

Prevalence of subclinical hypothyroidism among girls attending the gymnasia in the city of Starogard Gdański

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Introduction
Subclinical hypothyroidism (SCH) can impair concentration and memory skills. If this is a case among adolescents it may impair learning abilities, which in turn may be the cause of poorer performance on various tests and exams. Therefore, the aim of this study was to evaluate the prevalence of SCH in teenage girls attending the gymnasia in the city of Starogard Gdański.
Material and methods
In total 487 girls (age range 11.5–14.7 years) participated in this study. Five milliliter of venous blood was drawn and serum TSH concentrations were measured. In all the participants whose serum TSH concentrations were in the 3rd tertile ($>$ 2.7 mU/l) serum concentrations of fT_4, anti-thyroid peroxidase (ATPO) and anti-thyroglobulin (ATG) antibodies were measured as well as the ultrasonography of their thyroid gland was performed ($n=122$).
Results
Serum TSH concentrations ranged from 0.18 to 55.76 mU/l (median 2.21 mU/l) and the calculated reference range was 0.94–4.31 mU/l. Serum TSH concentrations $>$4.31 mU/l were found among 5.5% ($n=27$) of our participants. Subjects with serum TSH $>$ 4.31 mU/l had a significantly lower body weight and height compared to those with serum TSH concentrations $<$4.31 mU/l. There was also a smaller percentage of girls after menarche among the subjects with serum TSH $>$4.31 mU/l (40.7 vs 62.6%, $P=0.023$). In the USG of the thyroid gland, 54.1% of the subjects with serum TSH $>$ 2.70 mU/l presented decreased echogenicity. Serum levels of ATPO and ATG were elevated in 12.3 and 10.9% of girls, respectively and correlated significantly with the serum TSH concentrations ($P<0.01$).
Conclusions
The prevalence of SCH in our cohort was 5.5%. Compared with girls whose serum TSH values were below the upper limit of the calculated reference range they had significantly lower body weight and height and were less likely to be after menarche. If this state of mild thyroid dysfunction can have an impact on their cognitive functions warrants further studies.

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P1072

Antiepileptic drugs and the thyroid hormone axis

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Introduction
Antiepileptic drugs may cause altered thyroid function in adults according to previous studies. The cllinical impact of this is unclear. The aim of this study was to evaluate thyroid function in patients taking antiepileptic drugs to evaluate a possible clinical impact.
Methods
Adult epileptic patients (older than 18 years old) who attended the neurology outpatient clinic at Landspitali University Hospital in Iceland (the only University Hospital in the country) from 1st of January 1998 to 31st of December 2011 were included in the study. Patients were excluded if they had any previous history of thyroid disease and/or if they had been taking epileptic drugs for $<$ 3 months. Information about medication, medical history and thyroid test results (serum free thyroxine (fT_4) and TSH) was gathered from medical reports. Patients were invited to undergo blood test if thyroid testing had not been done.
Results
165 patients were included, 73 men and 92 women. The mean age was 45.6 ($\pm$15.5) years. The mean serum TSH was 2.2 ($\pm$ 1.3) mIU/l, range $<$0.01 – 7.98 (reference value 0.30–4.20 mIU/l). The mean serum fT_4 concentration was 14.2 ($\pm$2.9) pmol/l, range 8.1–24.4 (reference value 12–22 pmol/l). Two patients had elevated TSH and low fT_4. Thirty-five patients had fT_4 below the reference range and normal TSH. Three patients had elevated fT_4 and a normal TSH. Twelve patients had elevated TSH and normal fT_4. Most patients found low in serum fT_4 and TSH levels complained of tiredness.
Conclusion
Low serum fT_4 is common in patients taking antiepileptic drugs and is not associated with TSH elevation, indicating central hypothyroidism. Further research is needed to determine whether thyroxine is an affective treatment in this patient population.

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P1073

Hyperthyroidism in a pregnant, previously hypothyroid patient

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Introduction
Graves' and Hashimoto's diseases are considered two extremes of the same autoimmune thyroid disease. Spontaneous conversion from hypothyroidism to hyperthyroidism is uncommon. On the other hand, Graves' disease typically

improves during pregnancy and worsens after delivery. We describe a patient with an unusual course of thyroid disease during pregnancy.
Case report
An 33-year-old woman, with a two-year history of hypothyroidism, treated with 75 μg of levothyroxine, presented in her 9th week of gestation with fatigue, sweating, palpitations and nervousness. Physical examination showed diffuse goitre, tachycardia (110 b.p.m) and distal tremor. Laboratory tests showed supressed TSH (<0.04; normal: 0.34–5 mU/l) and slightly increased free T_4 (1.66; normal: 0.6–1.6 pg/ml). Thyroid ultrasound showed global enlargement and an 8 mm hyperechoic nodule in the right thyroid lobe. Levothyroxine dose was halved and 2 weeks later, hyperthyroidism had worsened (TSH 0.01 mU/l, free T_4 4.22 pg/ml, total T_3 3.9 ng/ml and normal 1–2.2 ng/ml). TPO and TSI antibodies were positive. Levothyroxine was stopped and propylthiouracil (PTU) (daily dose 100 mg) was started and further increased and reduced again in the second trimester. In the third trimester of pregnancy, TSH was still supressed, but T_3 and free T_4 were in the normal range. Cesarean delivery was performed at 41 weeks, which resulted in the birth of a healthy girl. Anti-thyroid treatment was continued and radioiodine (7.5 mCi) was given 1 year after delivery, due to persistent hyperthyroidism. Two months later, the patient developed hypothyroidism (TSH 20.99 mU/l and free T_4 0.15 pg/ml) and levothyroxine was resumed. Two years later, the patient is euthyroid on 50 μg of levothyroxine/day.
Discussion
Conversion of autoimmune hypo- to hyperthyroidism is exceptional during pregnancy. To our knowledge, there are only three cases previously reported. Routine and frequent assessment of thyroid function during pregnancy allows the diagnosis to be made assessment of thyroid function during pregnancy allows the diagnosis to be made. Levothyroxine dose was halved and two weeks later, hyperthyroidism had worsened (TSH 0.01 mU/l free T_4 4.22 pg/ml, total T_3 3.9 ng/ml and normal 1–2.2 ng/ml). TPO and TSI antibodies were positive. Levothyroxine was stopped and propylthiouracil (PTU) (daily dose 100 mg) was started and further increased and reduced again in the second trimester. In the third trimester of pregnancy, TSH was still supressed, but T_3 and free T_4 were in the normal range. Cesarean delivery was performed at 41 weeks, which resulted in the birth of a healthy girl. Anti-thyroid treatment was continued and radioiodine (7.5 mCi) was given one year after delivery, due to persistent hyperthyroidism. Two months later, the patient developed hypothyroidism (TSH 20.99 mU/l and free T_4 0.15 pg/ml) and levothyroxine was resumed. Two years later, the patient is euthyroid on 50 μg of levothyroxine/day.

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P1074

High-resolution thyroid nodule clinic: analysis of 1674 thyroid nodules

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Background and objectives
The finding of a thyroid nodule is a very common occurrence in clinical practice. Management of thyroid nodules requires a multidisciplinary approach that may be eased by a high-resolution thyroid nodule clinic. We report our clinical experience and outcomes in a high-resolution thyroid nodule clinic.
Materials and methods
We conducted a retrospective analysis of 1674 thyroid nodules evaluated in a high-resolution clinic from an academic hospital between 2005 and 2011. ATA and ETA guidelines were used for thyroid nodules assessment.
Results
Of these 1674 nodules, 64.2% were solid, 45.7% hypoechogenic, and 6.3% showed microcalcifications. Mean nodule diameter was 1.96 cm. Fine-needle aspiration (FNA) was performed in 1303 nodules, and 61 (3.6%) were cancerous. Mean nodule diameter was similar between benign and malignant nodules (2.46 vs 2.58 cm, $P=0.13$). Increasing nodule size did not impact cancer risk.
Conclusions
In this cohort of 1674 thyroid nodules, most nodules were solid and hypoechogenic. Thyroid cancer prevalence was 3.6% and cancer rate was not associated with thyroid nodule size.

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P1075

Cardiothyreosis in female with overt hyperthyroidism

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Introduction
Cardiothyreosis (CT) is the most frequent and dangerous complication of hyperthyroidism (HT). It is defined as an association of HT with severe heart abnormalities such: rhythmic troubles, heart and/or coronary insufficiency, atrio-ventricular block, and arterial pulmonary hypertension.
Our aim was to study its frequency, in Algerian population, analyze its profile and its response to radical treatment.
Materials and methods
It is a retro- and prospective study (1981–2012) which took into account medical history, clinical examination, routine analyses, hormonal and heart explorations based on heart sonography, electro-radiography ± heart MRI and heart scintigraphy.
Results
Among 1680 females HT, 246 had CT = 14.64%. We observed 7.93 cases at year. Median age at diagnosis is 59 years (10–96). Five patients (2.03%) were under 30 years old. A high incidence was observed between 1991 and 1996 was probably due to salt iodization program. A personal background of heart diseases was observed in 61.78%. The main heart complications were arythmias (75%) and heart insufficiency (49.79%). The CT complicated essentially a toxic goiter in 68%, and secondary Graves' disease in 28%. Among 246 females CT, 35 were lost in sight before radical treatment, 172 were treated, 91 had surgical treatment with or without radio iodine and 81 had radio Iodine. Normalization of heart function was observed in 52.45% only.
Conclusion
CT is a life-threatening complication of HT is very frequent in Algerian women, risk factors for poor prognosis were: old age, toxic goiter and Personal or family background of heart diseases.

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P1076

Therapeutic options for Grave's disease and toxic nodular disease: experience of an endocrinology department

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The thyroid pathology is an area of special interest in our department. Hyperthyroidism represents 3.4% of the 8144 patients followed.
The aim of this study is to characterize the therapeutic approach in patients with Grave's disease (GD) and toxic nodular disease (TND).
Retrospective study of 217 patients diagnosed with GD and TND, evaluated according parameters of therapeutic option, efficacy, relapse rate and associated complications at 6 months and 1 year. Variables were analyzed by methods of descriptive statistics: frequency and contingency tables for categorical variables and mean, s.d., minimum and maximum for continuous variables. From 217 patients, 138 were included in the study (91 GD and 47 TND). In TND 68% were female, aged 59.5 ± 13.2 years. GD 75% were female, aged 42.69 ± 15 years.
In both diseases the decision for surgical treatment was chosen, respectively, in 48.9 and 2.8% of the medical cases. Treatment with radioactive iodine in 40.4 and 19.7% and anti-thyroid drugs (ATD) in 10.6 and 77.5% of cases.
All patients that underwent surgical treatment remain euthyroid at the end of 1 month, with no recurrence after 12 months. Average dose of iodine in TND was 9.5 mCi, with 89.4% achieving euthyroidism at 6 months, with 20% of recurrences at 12 months and 15.7% became hypothyroidism.
Average dose of iodine in GD was 11.5 mCi, achieving 71.4% euthyroidism in 6 months, 11.8% recurrences at 12 months and 16.7% became hypothyroidism. With ATD became Euthyroidism, 80% (for GD) and 81.5% (for DNT) with 25% recurrences 25% in GD and 45.7% in DNT at 12 months.
The treatment of choice was the surgical approach to TND and ATS for the GD, with recurrences rates similar to those of the literature <1% with surgery, 50% ATD and 20% with iodine.

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P1077

A typical clinical manifestations of Graves' disease

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Hyperthyroidism is a common medical disorder that is not infrequently overlooked or misdiagnosed. Hyperthyroidism presents with multiple symptoms that vary according to the age of the patient, duration of illness, magnitude of hormone excess, and presence of co-morbid conditions. Over the last few decades, there are increasing numbers of reports of newly recognized manifestations of hyperthyroidism that are related to various body systems and may create a wide range of differential diagnosis. Lack of knowledge of the association between these findings and hyperthyroidism may lead to delay in diagnosis, misdiagnosis, or unnecessary investigations. Of the atypical manifestations of Graves' disease, we have chosen anemia, vomiting, jaundice, and right heart failure to discuss. These manifestations were selected because each of them represents a very common clinical condition and they can be attributed to a wide variety of hematological, gastrointestinal, and cardiopulmonary causes. The presentation is based on clinical practice real life cases from which we move to the atypical manifestation in focus.
I describe four cases, three of them have been published.
I also prepared the slides based on a literature review and on an article of my own 'A typical Clinical Manifestations of Graves' Disease An Analysis in Depth'.
I received the first email from ECE only 4 days ago and I had no time to prepare before the deadline. I have prepared the PowerPoint presentation very quickly, but it will be much improved at the time of presentation.

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P1078

Evaluation of cardiovascular risk factors in adults with primary hypothyroidism

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Introduction
Hypothyroidism is a frequent pathology responsible for a significant increase in cholesterol. It is caracterized by myocardial changes, increased risk of cardiovascular disease and more particularly coronary event performance.
Aim
Assess cardiovascular risk factors in adults suffering from primary hypothyroidism.
Materials and methods
This retrospective study included data from 50 patients (44 women and 6 men) adults (age >18 years) with primary hypothyroidism acquired(non iatrogenic) whose average age at diagnosis was 47.6 years (aged 19–75) initially before prescription replacement therapy.
Results
The BMI was 27.84 kg/m^2 with obesity in 43.3% of cases and 13% overweight. The mean cholesterol is 2.01 g/l and 23.3% of patients have high cholesterol, triglycerides means of 1.37 g/l and 20% of patients have a hypertriglyceridemie. 26.6% of patients have hyper blood pressure (hypertension) and 10% had diabetes mellitus type 2. coronary artery disease is diagnosed in 13% of cases and was significantly associated with age and hypertension.
Conclusion
The thyroid hypofunction is the cause of lipid disorders that enhances cardiovascular risk and increases morbidity and mortality. Atherosclerosis is more severe because it associates with several cardiovascular factors.
Our highlight of results frequency of overweight, dyslipidemia, hypertension and diabetes mellitus. They must be systematically sought and reassessed in euthyroidism.

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P1079

Optical neuropathy and Graves' disease

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Introduction
Graves' disease is rare but may be complicated by major eye signs of Graves' series rarely causing paralysis of the optic nerve.
Aim
Report cases of seven patients collected between 1982 and 2013 presenting Graves' disease complicated by optical neuropathy.
Observations
Men patients aged on average 44 years old (35–48), admitted for Graves' disease complicated by ophthalmopathy with oculomotor paralysis. signs of eyes showed disease in three cases. Among other cases, neuropathy occurred during follow-up. They presented goiter Ib and II, nodular ultrasound in 4cases with signs of hyperthyroidism. The exophthalmia was averaged 20 mm for OG (18–22) and 22 mm (20–23) for the OD, not reducible with lid retraction. There was oculomotor paralysis with limitation of abduction and the adduction of the eye up and down and a diplopia. The fundus papillary showed pallor in all cases and the scanner orbital thickening internal muscle structures of the upper and lower extended their ocular insertion apex. the major thickening compressing the optic nerves.
The patients were put under solumedrol IV bolus followed by 1 mg/kg per day of Prednisone for 6 weeks and a maintenance of 10 mg/day dose for 6 months associated with Carbimazole for 2 years. The evolution of ophthalmia was spectacular with regression of oculomotor paralysis and exorbitism in a year and a half (1–3). All patients were in remission with a decrease of 8 years on average.
Discussion and conclusion
The Graves' optic neuropathy is a rare and major complication. When the diagnosis and its management are late, patients are exposed to serious ocular sequelae. The particularity of our observations is the dramatic and relatively rapid regression of eye signs.

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P1080

Associations of thyroid function and autoantibodies with parameters of oxidative stress in women with Hashimoto's thyroiditis

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Objectives
Patients with thyroid dysfunction due to AITD have been found to have increased oxidative stress. Possible associations of oxidative stress with thyroid hormone (TH) and thyroid autoantibodies (ThAb) levels in euthyroid patients with autoimmune thyroiditis have not been adequately studied. We examined possible associations of oxidative stress markers with TH levels and with the presence of ThAb in euthyroid women with Hashimoto's thyroiditis (with or without T_4 replacement).
Methods
A total of 298 women were examined: 208 women with ThAb (+) (mean age 47.9 ± 11.5, range 22–69 years, group 1: 100 euthyroid and group 2: 108 on T_4 replacement). 90 women with ThAb (−) and negative family history for AITD served as controls (mean age 43.6 ± 12.9, range 19–67). The type of food, the frequency and the way of cooking was filled and the weekly diet antioxidative score (DAS) was calculated. Peroxide lipid levels (index of oxidative stress, TOS) and the calculated diet antioxidative score were estimated.
Results
DAS was inversely associated with TOS ($r=-0.11$, $P=0.049$). Mean DAS was lower in women with anti-TPO (+) vs anti-TPO (−): (167.9 ± 47.5 vs 181.7 ± 55.0, $P=0.031$, Mann–Whitney U test). Multivariate logistic regression analysis showed that TPO positivity was significantly associated with DAS ($P=0.044$ or 0.995) when age, TSH and smoking were taken into account. No difference in TOS according to TPO positivity was found. TOS was positively associated with T_4 ($r=0.137$, $P=0.001$). This association remained significant when TSH, anti-TPO positivity and age were taken into account. TOS was positively associated with T_3 levels ($r=0.190$, $P=0.001$); however this was no longer

significant in the multivariate analysis. No significant difference concerning TOS was found between women on or without thyroxine replacement therapy.
Conclusions
Diet with lower antioxidant score may be a predisposing factor for the development of thyroid autoimmunity (TPO positivity). TOS is positively associated with TH levels even in the normal range as has been previously shown in the hyperthyroid state. No association of anti-TG Abs with oxidative parameters was found.

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P1081

Involvement of Lat2 in the transport of 3,3′-T2 across the plasma membrane and first structural insights into transport mechanisms by homology model generation

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Thyroid hormones (THs) are transported into their target cells by diverse transmembrane transporter proteins, e.g. by members of the L-type amino acid transporter (LAT) family. The Lat2 is a sodium independent amino acid exchanger and interacts with CD98 for its efficient cell surface expression. So far the role of Lat2 in TH transport including the transport mechanisms is unclear. It is important to determine TH subtype specificity and to identify amino acids at Lat2 which are involved in the substrate recognition and transport.
By using *Xenopus laevis* oocytes as expression system we could demonstrate a noticeable increase in 3,3′-T2 and to some extent also in T3 uptake by Lat2. We are able to induce the specific 3,3′-T2 uptake by Lat2 coexpressed with CD98. The 3,3′-T2 uptake is sodium independent and the calculated KM value is in a low micromolar range. To gain insight into properties of THs transported by Lat2 we used TH derivatives differing in their number of iodine atoms and could show a strong competition on 3,3′-T2 uptake by THs like 3-T1 and other T2 derivatives. In addition, the transport mechanisms by Lat2 are unknown and neither a molecular structure nor a homology model is available. Therefore, we generated the first molecular homology model of Lat2, which is based on two X-ray structures, arginine/agmantine antiporter (AdiC) and amino acid polyamine and organocation transporter (ApcT). We verified our model with published functional features and *in vitro* transport studies of Lat2 mutants.
In conclusion, our results demonstrate that Lat2 is involved in 3,3′-T2 transport and might contribute to termination of TH action. Furthermore, for a better understanding of transport mechanisms for TH influx and efflux in cells we will use our molecular model to identify TH recognition patterns.

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P1082

A Sensitive LC/MS/MS Method for the Quantification of Free T3 and Free T4 in Serum, using a Simple Ultrafiltration Sample Preparation

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Introduction
The measurement of free thyroxine (FT4) and free 3,3′,5-triiodothyronine (FT3) in serum by equilibrium dialysis immunoassay methods may suffer from a lack of specificity, therefore measurement by LC/MS/MS has the potential to increase the accuracy of the results. Here we present a sensitive method, employing a simple ultrafiltration sample preparation.
Description of methods
400 uL of serum were processed for 90 minutes using a 3kDa centrifugal filter, and 50uL of the ultrafiltrate was directly injected onto an AB SCIEX Triple Quad® 6500 LC/MS/MS system.
Results
The method presented here achieved a Limit of Quantitation (LOQ) of <0.5 pg/mL for both FT3 and FT4, and demonstrated excellent linearity, accuracy and precision over the concentration range from 0.5 pg/mL to 100 pg/mL. A method comparison was performed, using a cohort of samples that had been previously analyzed by immunoassay, and an excellent correlation was obtained.
Conclusion
We have demonstrated a sensitive method for the analysis of FT3 and FT4 in serum by LC/MS/MS, which takes advantage of the simple and rapid sample preparation afforded by ultrafiltration. The method provides good sensitivity, accuracy and precision, enabling researchers to investigate FT3 and FT4 levels in serum across the expected range of concentrations. Unlike earlier MS-based methods, this method does not require a large sample injection volume, since only 50 uL of the final sample is required.

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Thyroid Cancer

P1083

Langerhans cell histiocytosis and papillary thyroid carcinoma

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Introduction
Thyroid gland involvement by Langerhans Cell Histiocytosis (LCH) is a very rare condition. It occurs by thyroid infiltration that may result in hypothyroidism. LCH may be also related to neoplastic processes such as leukemias or lymphomas. However, the association with papillary thyroid carcinoma (PTC) is exceptional. We introduce a case and review the reported cases of this association.
Case report
We describe a 33 year old patient diagnosed of LCH with lung involvement and diabetes insipidus, which had a primary hypothyroidism by histiocytosis infiltration. During the follow-up, the patient develops a thyroid nodule. The neck ultrasound was suspicious and the fine needle aspiration confirmed PTC. Thyroidectomy was performed. A very invasive CPT mass was encountered, simultaneously with infiltration by the histiocytosis and a lymphocytic thyroiditis. Immunohistochemical studies were performed, revealing CD1a and S100 immunoreactivity in the Langerhans cells and the BRAF oncogen was positive.
Conclusions
There are few cases reported of patients affected by LCH and CPT. Both process could have common pathways in their pathogenesis. The underlying inflammatory process and BRAF mutation, could be the start point for CPT development, in generally more aggressive in this entity. Therefore is essential early diagnosis with routinely thyroid ultrasound.

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P1084

Thyroid carcinoma in cases with end stage renal disease

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Premilinary
The incidence of thyroid disease in cases operated for hyperparathyroidism is 2.5–17.6%. The coexistence of thyroid and parathyroid nodules makes FNAB difficult in technique but also in cytology diagnosis. Scintigraphy, unless performed with Tc SESTA MIBI, might give unclear informations.
Material
From series of 36 operaed cases with renal secondary and tertiary hyperparathiroidism, we identified four cases with concomitant thyroid papillary carcinoma.
Method
Preoperative evaluation in all cases: clinical, 2 B ultrasound, Power Doppler, and real-time elastography with qualitative and computer assisted quantitative measurement of tissue elasticity with high accuracy linear probe, Hitachi E 7500 Device, Hitachi, Inc., Japan. Histopathology evaluation was performed in all cases. FNAB was performed in cases with associated thyroid nodules.
Results
Histopathology evaluation confirmed the association of thyroid carcinoma (papillary carcinoma) and parathyroid nodular hyperplasia in four cases. These cases consist of three women (aged 57 and 61), and two men (40 and 42 years), with end stage renal disease, in choric hemodialysis program for mean period of 4.65 ± 1.15 years.

Preoperative imaging showed proper localization of the hyperthophic/hyperplasic parathyroid glands but also proper description on the thyroid nodular disease. Ueno score 3 and 4 was observed in all four cases of thyroid cancer. The qualitative suspicion was confirmed by an increased strain ratio in suspicious thyroid nodules, compared with unsuspicious thyroid and parathyroid nodules.
FNAB was impossible in one cases (para-carotidian nodular position). Citological results: two Bethesda 4, one unclear diagnostic. Total thyroidectomy was proposed in all the four cases.
Histopathological report confirmed the thyroid cancer suspicion.
Conclusion
Elastography brings important data in respect to different types of nodular aspects described by conventional ultrasound. It may be used in differentiation of difficult cases with nodular intra and extra-thyroidal masses, where FNAB can not be easily used.

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P1085

The deleterious effect of levothyroxine (T_4) withdrawal on the degree of lipid profile change during follow-up of patients with differentiated thyroid cancer (DTC)

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Introduction
The degree of dyslipidemia caused by iatrogenic hypothyroidism is not clear in DTC. Therefore, we investigated the average of lipid profile change caused by LT_4 withdrawal in the follow-up of DTC.
Method
We enrolled 84 DTC patients who underwent high-dose RAI therapy for the treatment of recurred or remnant DTC and we measured serum levels of total cholesterol, triglyceride, LDL, and HDL and then analyzed changes in them according to the LT_4 withdrawal. Moreover, we also compared the results of TSH-stimulated Tg with anti-Tg antibody and I-131 scan with sole radiologic evaluation including neck sonography.
Results
The mean degree of the increase following LT_4 withdrawal in serum levels of total cholesterol, triglyceride and LDL was 70.51 ± 11.4, 87.9 ± 23.3 and 44.4 ± 9.4 mg/dl, respectively. Of the 84 patients, 29 were suspected of having tumor recurrence or remnant and they underwent repeated high-dose RAI or re-operation. However, there were no changes in the management of other 65 patients because their levels of TSH-stimulated Tg was below 1 ng/ml following LT_4 withdrawal and they had no remnant or recurred disease on imaging studies. Furthermore, despite a lack of the data about T_4 withdrawal Tg/anti-Tg anti-body, all the remnant DTCs could be detected solely by radiological assessments in the re-treated 29 cases.
Conclusion
Our results re-confirmed that iatrogenic hypothyroidism was associated with a significant increase in atherogenic lipid levels and this study showed the mean degree of the derangement of lipid profiles by T_4 withdrawal in patients with DTC at first. In addition, it was also shown that TSH stimulated Tg could not show the more efficient detection in the DTC recurrence compared to sole image modalities even though in the high risk patients of DTC recurrence or remnant.

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P1086

Symptomatic hypercalcemia due to primary hyperparathyroidism by parathyroid carcinoma

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Parathyroid carcinoma is a rare cause of primary hyperparathyroidism. Clinical suspicion is determined by the severity of hyperparathyroidism associated or not with palpable cervical tumor and local invasion when surgery.

Case report
A 45-year-old woman without any previous history of kidney stones or fractures. Admitted to hospital because of high hypercalcemia (calcium 15.1 mg/dl), fatigue and generalized arthralgia. Physical examination revealed right thyroid nodule about 3 cm. Cervical ultrasound: RTL nodule 3×2 cm without lymphadenopathy. Sestamibi Scintigraphy-CT enhanced uptake at this level suggestive of right parathyroid adenoma. Biochemistry revealed PTH 548 pg/dl, Calcium 10.9 mg/dl, phosphorus 1.76 mg/dl, vitamin D 7.71 ng/ml, creatinine 0.9 mg/dl. Renal ultrasound: emerging nephrocalcinosis. DEXA scan showed osteoporosis. Primary severe hyperparathyroidism was suspected. She was referred to neck surgery team, performed right hemithyroidectomy. Histopathology revealed 3.2 cm parathyroid carcinoma infiltrating thyroid and adjacent adipose tissue, with 5% ki 67 and free disease surgical borders. After surgery: PTH 42.11 pg/ml, Calcium 8.6 mg/dl, Phosphorus 2.89 mg/dl, vitamin D 10.5 ng/ml and TSH 7.22 μUI/ml. She started bisphosphonate therapy, calcifediol and levothyroxine 50 μg/day. Neck US showed right thyroid lobectomy without thyroid remnants or suspicious lymphadenopathy. Subsequent blood tests displayed hypocalcemia and hypophosphoremia, suggestive of 'hungry bone syndrome', started treatment with calcium carbonate and calcitriol. Genetic testing for HRPT2 was requested with negative result and PET-CT didn't evidence active neoplasic disease.
Conclusion
The fast decrease of serum calcium after surgery is consider as a surgical marker of success. It is also risk factor for developing 'hungry bone syndrome'. Because of possibility of recurrence to medium-long term, they require lifelong surveillance. The possible association of parathyroid carcinoma with jaw ossifying fibromass been rejected due to the negative result on genetic study.

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P1087

Incidence of thyroid microcarcinoma in relation to gender and age in non-toxic thyroid diseases treated with total thyroidectomy

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Aim
Thyroid cancer comprises the most common endocrine malignancy and a variety of studies have examined the incidence of microcarcinomas in benign 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 microcarcinoma in a patient cohort with non-autonomous thyroid disorders and without cytological establishment of cancer who underwent total thyroidectomy.
Patients-methods
Between 1.1.2005 and 01.03.2010 186 patients (146 females/40 males) underwent total thyroidectomy because of nodular goiter in our Department. The classification of patients in both genders was conducted in the following age-groups: $a = 20$–39 y, $b = 40$-59 y, $c = > 60$ y. Thyroid specimens were histopathologically examined at the University Pathology Department for the establischment of the final diagnosis of benignity or malignancy. Thyroid cancer cases were categorised in relation to gender and age group.
Results
32 patients (17.2%) were diagnosed with microcarcinoma (rate females:males 2.2:1), while 154 patients (82.8%) were free of malignancy. The incidence of thyroid cancer in male subjects was 25.0% (10/40) and mainly in the subgroup of solitary nodule compared to multinodular goiter (41.67 vs 17.86%). The respective cancer freguency in female subjects was 15.0% (22/146). The incidence of microcarcinoma per age group was in males: $a = 4/9$; 44.4%, $b = 1/15$; 6.67% and $c = 5/16$; 31.25% ($P = 0.089$). In females it was respectively: $a = 7/40$; 17.5%, $b = 9/73$; 12.3%, $c = 6/33$; 18.2% ($P = 0.650$).
Conclusions
Thyroid microcarcinoma shows an elevated incidence in males with non-toxic goiter, especially in the age groups 20–39 y and > 60 y. Total thyroidectomy appears to be the therapeutic method of choice in men with indication of surgical removement of an euthyroid goiter which belong to the above age groups. Contrarily, there is no statistically significant variation of microcarcinoma incidence in women with benign thyroid disorders in relation to age.

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P1088

Estimated 10-year risk of bone fracture in women with diffentiated thyroid cancer on TSH-suppressive levo-thyroxine therapy

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After thyroidectomy (Tx) and RAI therapy, patients with diffentiated thyroid cancer are treated with levo-thyroxine to suppress TSH levels. Whether hyperthyroxinemia causes osteoporosis is debated. The aim of this study was to evaluate bone mineral density (BMD) and the fracture risk assessment tool (FRAX) in DTC women. FRAX calculates the 10-year probability of hip fracture (HF) and major osteoporotic fracture (MOF) in subjects aged >40. 46 women with DTC diagnosed and treated (Tx 96%, RAI 72%) at the age of 52.4±10.3 years were studied. L-T_4 was started 58 mts before Tx for goiter in 15% of patients. Baseline BMD measured by DXA of the lumbar spine and FRAX score calculated on femoral neck BMD were evaluated 2.5 years after diagnosis. The age at this time was 56.2±8.0 years and 76% of patients were postmenopausal. BMD and FRAX evaluations were repeated after 5.5 years. Neck sonography and thyroglobulin levels indicated a disease-free condition at each experimental time. L-T_4 dosages were 809±229 μg/week and 790±153 μg/week at the baseline and 2nd evaluation respectively. Results are reported as means±s.d. (medians in brackets) (Table 1).

Table 1

	Baseline	2nd evaluation	Significance
TSH (mU/l)	0.57±0.79 (0.23)	0.25±0.38 (0.10)	$P<0.001$
F-T_4 (pg/ml)	15.7±2.6 (15.7)	17.0±2.1 (16.8)	$P=0.01$
Time on l-T_4 (months)	66.6±62.1 (47)	132.2±73.2 (125)	$P<0.001$
BMD (g/cm ^{2})	0.930±0.174 (0.901)	0.939±0.170 (0.898)	NS
HF (%)	0.9±1.2 (0.6)	1.3±1.3 (1.1)	$P<0.001$
MOF (%)	4.5±2.6 (3.9)	5.6±3.1 (5.3)	$P<0.001$

Adequate TSH levels under moderate hyperthyroxinemia were more often observed on follow-up than on baseline evaluation, without significant changes in BMD. Significant changes in FRAX were found from the baseline to the 2nd evaluation, with the probability of HF increasing more than that of MOF. A significant inverse correlation ($P<0.01$) emerged between L-T_4 dosage and HF/MOF probability, both at the baseline and the 2nd evaluation, while a further slightly significant inverse correlation ($P=0.05$) was found between F-T_4 levels and HF/MOF probability only at the 2nd evaluation. In conclusion, FRAX increase seems to be an age-related multi-factorial phenomenon. In DTC women, lumbar BMD does not change as much as FRAX. The absence of positive correlations between L-T_4 dosage, length of therapy or F-T_4 levels and FRAX does not allow us to attribute an increased fracture risk to DTC women with well-controlled disease. A larger population of DTC patients and a longer period of observation may yield more conclusive data.

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P1089

Prognosis and outcome analysis of thyroid cancer: experience from a tertiary care centre in Pakistan

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Material and methods
Retrospective review of patients with thyroid cancer at our hospital from 1999 to 2011 was done.
Results
Mean age at presentation was 44±17 years with female to male ratio of 2.1:1. Patients were followed for mean of 6.45 and median of 6 years. Out of 206 patients, 158 had differentiated thyroid carcinoma. Most common variant was papillary ($n=130$, 63.10%) followed by follicular carcinoma ($n=22$, 8.73%). 6 (2.91%) had hurthle cell variant of follicular carcinoma. 18 (8.73%) had medullary and 10 (4.85%) had anaplastic carcinoma. 20 (9.70%) patients had other causes like carcinoma of undetermined significance, metastatic carcinoma and lymphoma.
Patients having DTC, 70 (44.3%) were diagnosed at stage 1, 17 (10.8%) at stage 2, 12 (7.6%) at stage 3 and 29 (18.3%) have stage 4 disease. 2 (14.3%) patients with medullary carcinoma were diagnosed at stage 1, 4 (28.6%) at stage 3 and 8 (57.1%) were at stage 4. All patients with anaplastic carcinoma had stage 4 disease. Overall cure rate was 33.5%, persistence rate 26.6%, recurrence was 8.2% and thyroid cancer related mortality was 8.9%.
By univariate analysis age, cancer types, distant metastasis, type of surgery and thyroglobulin levels were significant prognostic factors. By multivariate analysis age ≥ 45 years ($P=0.04$), distant metastasis at the time of presentation ($P=0.04$), thyroglobulin levels ≥ 8 right after surgery ($P\leq 0.001$) were found to be independent prognostic factors. Furthermore, other factors like gender and thyroglobulin doubling time did not show any association with the prognosis of thyroid carcinoma.
Conclusion
The current study demonstrated an assessment of prognostic factors in this cohort. Age at diagnosis, distant metastasis and thyroglobulin levels were found to be strong prognostic factors for thyroid carcinoma.
Keywords
thyroid carcinoma, stage, outcome
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P1090

Sentinel lymph node biopsy in thyroid papillary and medullary microcarcinomas

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Introduction
The aim of this study was to determine whether sentinel lymph node (SLN) biopsy of jugulo-carotid chain (JCC) in thyroid microcarcinomas (TMC) is an accurate technique to select patients with true positive, but clinically and ultrasonically N0 LNs, for modified radical neck dissection (MRND).
Materials and methods
In total 199 patients with TMC underwent total thyroidectomy, central neck dissection and SLN mapping with 0.2 ml of 1% methylene blue injected in thyroid gland. SLNs, identified in JCC, were examined by frozen section as a determination factor for additional MRND. All data were statistically analyzed.
Results
In our study, 93% of patients had papillary TMC, 6% medullary TMC, while 1% had these two combined. Definitive pathohistology showed a 96.48% match with frozen-section analysis results – a total of 21 (10.55%) patients with papillary TMC had positive SLNs, with no false-positive findings. They were treated with MRND of the positive JCC, additionally to total thyroidectomy and central neck dissection. Analysis showed more frequent lateral metastases in patients with tumors 5 mm or less in diameter (12.88%) than in larger ones (7.46%). Method's accuracy is 95%.
Discussion and conclusions
Data showed that SLN biopsy precisely determines patients with lateral neck compartment metastases, even if clinically and ultrasonically staged N0. Tumor size cannot predict lateral metastases. There were no LN metastases in medullary TMC. Using SLN biopsy for intraoperative assessment of lateral LN one can avoid unnecessary MRND. In addition, this method helps optimizing ablative radioiodine treatment.

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P1091

Surgical treatment of papillary thyroid carcinoma in children and adolescents

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Background
Papillary thyroid carcinoma in children and adolescents is rare but it shows aggressive behavior. Gross lymph node metastases and distant metastases are common on first clinical presentation.

Patients and methods
Forty-eight children and adolescents were operated due to PTC. Mean age was 16.6 years (range 7–21). At the time of diagnosis 13% had lung metastases. Total thyroidectomy or completion of thyroidectomy was performed in all cases followed with central neck dissection and frozen section examination of lower jugulo-carotid compartments.
Results
Median tumor size was 1.9 cm. PTC was found in 47 and FTC in one patient. Multifocal tumors were found in 37% and capsular invasion in 29% and vascular invasion in 24% of cases. LNM in either central or lateral neck compartments were found in 76% of patients. Capsular and vascular invasion were significantly more frequent in children <16 years of age. Median follow-up was 127 months. Overall survival rate was 100%.
Conclusion
PTC in children and adolescents is characterized with high incidence of loco-regional aggressiveness, multifocality, lymph node metastases, and distant metastases at the time of diagnosis. Adequate surgical approach, total thyroidectomy, central neck dissection, and uni/billateral MRND when indicated, should be performed in both primary and recurrent disease in young patients with PTC.

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P1092

Correlation between biochemical and ultrasound parameters in patients with single parathyroid adenoma

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Aim
The aim of this study was to determine the relationship of the biochemical parameters serum phosphate, serum calcium, and serum parathyroid hormone levels with respect to parathyroid adenoma weight and volume in primary hyperparathyroidism.
Methods
Data were collected retrospectively from patients with primary hyperparathyroidism, who were diagnosed and followed between 2008 and 2013. 26 patients (female/male: 23/3) with a mean age of 51.3 ± 12.7 years were enrolled into the study. Single parathyroid adenomas were identified from ultrasound examination reports. Preoperative calcium, phosphate, and parathyroid hormone levels were collected from charts. The data were analyzed using a multiple ANOVA, and a correlation coefficient was calculated. The level of significance was set at $P \leq 0.05$.
Results
With respect to adenoma volume, there was a significant correlation with serum calcium and parathormone levels ($P=0.0001$ and $P=0.0001$ respectively). There was no significant correlation between serum phosphate and adenoma volume. With respect to adenoma weight, there was a significant correlation with serum calcium and parathormone levels ($P=0.0001$ and $P=0.0001$ respectively). There was no significant correlation between serum phosphate and adenoma weight.
Conclusions
Preoperative serum calcium and parathormone levels may be able to predict adenoma weight and volume in primary hyperparathyroidism for a single adenoma.
Keywords
parathyroid adenoma, parathyroid hormone, primary hyperparathyroidism.
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P1093

Atorvastatin medullar thyroid cancer over TT cell line impact of apoptosis and calcitonin over gene expression

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Medullar thyroid cancer (MTK) approximately constitutes 5% of thyroid cancer, over the 25% cases it progresses in familial form. In charge of genetic inherited clinical features in RET protooncogene 'germ-line' makes up activating mutations. In post RET mutation in association with tyrosine kinase activation oncogenic cell proliferation is increased. In medullary thyroid cancer persistent and recurrence disease management is complicated, because it is unresponsive toward chemotherapy, radiotherapy, and radioactive iodine therapy. In these cases, RET and tyrosine are termed as the agents targeting kinase receptor activity. Tyrosine kinas inhibitors may be potential to stabilize metastatic disease, but in terms of survival time period they do not lead to any variation and due to widespread of side effects their clinical administration remains difficult. Stains inhibiting mevolanat channel by HMG Co A reductase inhibition, based on proapoptotic, antiangiogenetic, and immunomodulatuar effect were identified to be able to cancer cell growth in previous plenty of studies. In the present study, throughout TT cell line we investigated atorvastatin's apoptotic impact in cancer cells and calcitonin's variation gene expression.
TT cell's administered in atorvastatin varying doses (12.5–25–50–60–70–80–90–100–125–150–200 μM) and at 24. Hours IC 50 ratio accounted 90 μM, 48. Time IC 50 value 80 μM and at 72. Hours IC 50 value calculated as 80 μM. Atorvastatin's apoptotic effect; evaluated in correlation with caspase 9 activity. In comparison with atorvastatin's control cohort at 24. Hours 1.273-fold, at 48. Hours 1.660-fold and at 72 h 1.716-fold caspase 9 activity found to proliferate. In post atorvastatin calcitonin gene expression, compare to control cohort at 24. Hours identified to attenuate 1.377-fold, at 48. Hours identified to attenuate 7.290-fold and at 72. Hours identified to attenuate 8.494-fold. Eventually; atorvastatin along the TT cell line as dependent on dose and time increase apoptosis and calcitonin alleviate gene expression. Owing to atorvastatin easy clinical use and lesser side effects in the therapy of progressed MTK cases it may be deemed as a promising new agent.

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P1094

Anti-proliferative effects of evodiamine on human thyroid cancer cells

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Thyroid cancer is the most prevalent cancer among endocrine malignancies. Surgical resection combined with radioactive iodine therapy has been proved 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.
Compounds from traditional Chinese medicine have been examined for their anti-cancer potential in recent decades. Among them, evodiamine is one of the important components of Chinese herb Wu-Chu-Yu, and has been reported 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 anticancer effects of evodiamine in FTC, PDTC, and ATC cells respectively. Evodiamine inhibited cellular growth of FTC, PDTC, and ATC cells in a dosage-dependent and -time dependent manner. Moreover, cell cycle arrest at G2/M phase in all of the cells was also revealed under evodiamine treatment. In addition, evodiamine also induced apoptosis via up regulation of intrinsic and extrinsic pathways activation and PARP cleavage. Most importantly, evodiamine suppressed *in vitro* colonies formation and cell invasion of ATC cells was also determined. Our results demonstrate that evodiamine induces cell cycle arrest and caspase-dependent apoptosis leading to inhibit proliferation of multiple types of human thyroid cancer cells. It suggests that evodiamine could be a chemo-therapeutic candidate for human thyroid cancers.

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P1095

Differential miRNAs expression in papillary thyroid cancer is associated with clinico-pathological features and *BRAF* mutation

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Introduction
MicroRNAs (miRNAs) are short non-coding RNAs that regulate translation or degradation of target mRNAs. Therefore, miRNAs control gene expression in many biological processes, including proliferation, apoptosis, and differentiation. Deregulation of miRNAs expression is an important contributor to tumour development and progression. Even though several genetic and epigenetic lesions have been identified in human thyroid cancer, particularly in the papillary histotype (PTC), they lack conclusive prognostic value. The present study was undertaken to examine whether a differential expression of miRNAs could provide a tool to improve prognosis in PTC.
Design
The miRNAs expression profiles were examined using next-generation deep sequencing in 35 snap–frozen tissues from surgically removed PTC and nine normal thyroid samples. First, TMM and Benjamini-Hochberg's methods validated the miRNAs sequences used in the final statistical analysis. The Neyman type A gene-wise modelling was used to detect the existence of statistical significance differences in miRNA expression levels between PTCs and i) normal thyroid tissue, ii) PTC carrying a *BRAF* mutation and iii) PTCs outcomes. The latter was analyzed comparing cases of poor prognosis (recurrence/metastases) vs those with a recurrence free-time of at least 4 years.
Results
Out of the 670 miRNAs examined, 168 miRNAs were differentially expressed in PTC compared with normal thyroid tissue. In *BRAF* mutated-PTC, there were 47 miRNAs significantly deregulated compared with non mutated-PTC. More significantly, only 8 miRNAs were differentially expressed in cases with a recurrence-free time of at least 4 years compared to cases with a poor prognosis (adjusted $P<0.05$, fold change $\leq 0.5 - \geq 1.5$).
Conclusion
These findings suggest that miRNAs expression profiles could provide a useful tool to discriminate not only PTC from normal thyroid tissue, but also cases with poor prognosis.

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P1096

Ultrasound risk factors of thyroid cancer

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Differentiated thyroid cancer (DTC) is a relatively mild disease if detected early. The aim of the study was ultrasound evaluation of thyroid gland, selection of thyroid nodules with high chances of malignancy, and their verification in fine-needle aspiration (FNA), as well as assessment of TSH concentration and antiTPO titre.
The study involved 100 patients. DTC was diagnosed in 14 patients and undifferentiated or medullary thyroid cancer in two patients.
Cancer was diagnosed in seven out of 21 (33.3%) patients with normal thyroid size and in eight out of 71 (11.3%) patients with enlarged thyroid gland ($P=0.0162$)
The smallest nodule with positive FNA results had measurements of: 8 mm × 10 mm × 7 mm. The largest observed volume was a medullary thyroid cancer.
Papillary cancers had the lowest median volume.
Among 25 patients with a single nodule, 5 (20%) were diagnosed with cancer.
In patients with multiple nodules, cancer was diagnosed in 11 out of 75 (14.7%) ($P=0.5287$).
FNA was positive in 12 (19.1%) subjects with solid nodules and for 11 (14.7%) nodules with both solid and fluid parts ($P=0.3282$).
The nodules were hypoechogenic in all patients with positive FNA and in 58 (69.1%) patients with negative FNA ($P=0.0097$).
Microcalcification occurred significantly more often in positive-FNA patients ($P=0.0059$).
50% nodules with positive FNA had hypervascular central flow, in one case – intensive central flow, in two cases there was no flow in the nodules.
Positive FNA results were found in seven out of 15 (46.7%) patients with diabetes II and in nine out of 85 (10.6%) without diabetes ($P=0.0004$).
The following factors proved to increase the risk of thyroid cancer: hypoechogenic, solid, microcalcification, and increased central hypervascular flow nodules.
Diabetes significantly increased the risk of thyroid cancer. Enlarged volume of the thyroid gland and the number of nodules did not affect the probability of cancer.

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P1097

Do the poorly differentiated and undifferentiated thyroid carcinomas could be the next candidates to somatostatin analoques treatment?

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Introduction
The multimodal management of poorly differentiated thyroid carcinomas (PDTC) and anaplastic carcinomas (ATC) include surgical thyroidectomy, radioiodine treatment, and cytotoxic chemotherapy. Patients with distant metastases which do not respond to radiotherapy could be treated with new therapeutic possibilities like tyrosine kinase inhibitors. PPARγ or mutant P53 are also candidates to PDTC and ATC treatment. Somatostatin and its analogs, demonstrate antiproliferative, anti-angiogenic, and pro-apoptotic actions. The expression of the receptors in thyroid cancers was mainly investigated in medullary thyroid carcinomas (MTC), benign thyroid pathologies, and well differentiated thyroid cancers. In PDTC and ATC its presence has not been sufficiently explored. The aim of this study was to investigate the SSTR 1–5 expression in PDTC and ATC using immunohistochemical method and discuss their usefulness as an alternative to conventional forms of therapy.
Materials and method
The investigated group consisted of 18 archived thyroid cancer tissues: 14 PDTC and four ATC. The analysis of SSTR subtypes expression was performed by immunohistochemical method using rabbit polyclonal antisera raised against specific human somatostatin receptor subtypes and the Dako REAL EnVision Detection System.
Results
Analysis performed on 14 samples with PDTC revealed the equal expression of SSTR-1 and SSTR-5 with score ≥ 2.0 in 10 tumors (71.43%). SSTR-2A positive staining was observed in 5/14 (35.71%), SSTR-2B in 4/14 (28.57%), and SSTR-3 in 3/14 (21.42%) samples. Otherwise, the SSTR 1, 2B and five with score ≥ 2.0 were expressed in all ATC. SSTR 2A and 3 were observed in 50% of samples. The SSTR subtypes were localized in membranes and in the cytoplasm of tumoral cells.
Conclusions
The somatostatin multiligand or selective agonists should be considered as an alternative to conventional therapeutic agents in PDTC and ATC.

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P1098

Risk factors of cancer relapse in differentiated thyroid carcinomas

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Introduction
Reliable prognostic factors are crucial to choose the optimal treatment strategy and follow-up for differentiated thyroid carcinomas (DTC) patients. Thus, the aim

of the study was a retrospective evaluation of prognostic factors of cancer relapse in patients treated in a single institution.
Material
The study group consisted of 510 DTC patients, staged pT1b-T4N0-N1M0, treated with total thyroidectomy followed by complementary ^{131}I therapy. In 71% papillary thyroid carcinoma was diagnosed, whereas in 29% – follicular thyroid cancer. Based on TNM classification (revised 1997), 11.6% patients were classified as T_1, 35.1% – T_2, 8.4% – T_3, 9,4% – T_4, and 35.5% as Tx. Lymph node metastases (N1) were present in 24.7% cases. Median follow-up was 12.1 years (range 1.5–15.2).
Results
Age at diagnosis, sex, thyroid capsule infiltration, multifocal tumor growth, tumor size, N1, stimulated serum thyroglobulin (Tg) level, and ^{131}I thyroid remnant uptake evaluated before adjuvant ^{131}I treatment were statistically significant in univariate analysis. Stimulated serum Tg >30 ng/ml was the most important, independent risk factor in a multivariate Cox regression analysis, and increasing the risk of cancer recurrence nearly sixfold. N1 was associated with a nearly fourfold increase in the risk of relapse. Other independent poor prognostic factors in a multivariate analysis were tumor size, age at diagnosis, and thyroid remnant uptake before ^{131}I treatment. The risk of relapse in the study group was 12.55%. 5- and 10-year recurrence free survival were 90.1 and 87.5% respectively.
Conclusions
Serum stimulated Tg >30 ng/ml, measured after the surgery before radioiodine treatment, was the most significant independent prognostic factor. Age above 60 years, initial stage of the disease (tumor diameter and lymph node involvement) and low ($<1\%$) postoperative thyroid ^{131}I remnant uptake (T_{24}) independently increased the risk of relapse, whereas histopathological type and markers of tumor aggressiveness, such as thyroid capsule infiltration, multifocality, and angioinvasion did not influence recurrence free survival.

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P1099

DNMT1 expression in papillary thyroid carcinoma

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Introduction
In human cancer cells DNMTs are responsible for both *de novo* and maintenance methylation of tumor suppressor genes. Many studies have analyzed the relationship between the altered expression of DNMT1 and DNA methylation in cancer.
Aim
To analyze DNMT1 expression in thyroid papillary carcinoma.
Design
49 patients aged 10–82 years hospitalized for thyroidectomy were included between January 2013 and July 2013. The inclusion criterion was patients with thyroid nodules with indication for surgery and the exclusion criteria were: hyperthyroidism, medullary thyroid carcinoma, thyroid metastasis, other thyroid tumors, and anaplastic thyroid carcinoma. Patients were divided into three groups. Group 1: 26 subjects with papillary thyroid carcinoma. Group 2: 14 patients with follicular adenoma. Group 3: nine patients with multinodular goiter. Group 1 was divided in: Group 1.1- classical variant of papillary thyroid carcinoma, Group 1.2 follicular variant of papillary carcinoma; Group 1.3 diffuse sclerosing variant of papillary carcinoma. Total RNA was isolated from tissues and reverse transcribed. DNMT1 expression levels were investigated by qRT-PCR using Taqman (Applied Biosystem). Double normalization was performed related to gene expression levels found in peritumoral tissues. SPSS 18 (2010) program was used to perform statistical analyze. Results were compared using Kruskal–Wallis and Mann–Whitney *U* tests and were considered statistical relevant if $P<0.05$.
Results
DNMT1 gene expression in patients with papillary thyroid carcinoma was not increased comparing with controls ($P>0.05$). The comparison of cancer subtypes did not reveal significant differences for DNMT1. DNMT1 expression did not correlate with tumor stage, tumor multifocality, capsular, vascular or lymphatic invasion or with metastasis.
Conclusion
DNMT1 is not overexpressed in papillary thyroid carcinoma and does not correlate with tumor stage, tumor multifocality, capsular, vascular or lymphatic invasion or with metastasis.
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P1100

Methylation status of HOXB4 gene in papillary thyroid carcinoma

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Introduction
HOXB4 functions as a transcription factor involved in cell differentiation during embryogenesis and plays a role in apoptosis.
Aim
This study analyzed HOXB4 methylation status in thyroid papillary carcinoma.
Method
54 patients aged 10–82 years hospitalized for thyroidectomy were included between January 2013 and July 2013. The inclusion criterion was patients with thyroid nodules with indication for surgery and the exclusion criteria were: hyperthyroidism, medullary thyroid carcinoma, thyroid metastasis, other thyroid tumors, and anaplastic thyroid carcinoma. Patients were divided into four groups: Group 1: 26 subjects with papillary thyroid carcinoma, Group 2: 14 patients with follicular adenoma, Group 3: nine patients with multinodular goiter and Group 4: three patients with autoimmune thyroiditis. Methylation status of HOXB4 gene was assessed from normal thyroid tissue and tumoral tissue (thyroid carcinoma, follicular adenoma, multinodular goiter, and autoimmune thyroiditis) from the same patient. Total DNA was isolated from tissues and was treated with sodium bisulfite (EpiTect Bisulfite, and Qiagen) and was amplified using Direct Q-MSP. SPSS 18 (2010) program was used to perform statistical analyze. Results were compared using Kruskal–Wallis and Mann–Whitney *U* tests and were considered statistical relevant if $P<0.05$, excepting the situation when Bonferroni correction was used.
Results
In patients with thyroid carcinoma we observed a high level of methylation of HOXB4 gene in tumor tissue compared to peritumoral tissue ($P=0.0097$). The level of methylation of HOXB4 gene in tumor tissue is higher in papillary thyroid carcinoma than the follicular adenoma ($P<0.05$).
Conclusion
Analysis of the methylation status of HOXB4 gene showed a level of methylation significantly different between tumor and peritumoral tissue for the pathology investigated.
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P1101

The influence of polymorphisms in tumor suppressor genes in thyroid carcinomas

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Introduction
Thyroid carcinomas are the most often endocrine malignancy and their incidence is still growing. Thus, the finding of genetic predispositions to the thyroid cancer is desired. One of the genetic causes can be risk variants of tumor suppressor genes in patients. Our goal was to determine the influence of polymorphisms

Val109Gly (T/G) in gene CDKN1B encoding protein p27/Kip1 and Arg72Pro (C/G) in gene TP53 encoding protein p53 on the development of thyroid cancer. Both these genes are crucial in regulation of cell cycle.
Methods
Three cohorts were studied – 345 patients with sporadic medullary thyroid carcinoma (MTC), 269 patients with papillary thyroid carcinoma (PTC), and 374 healthy controls. DNA was isolated from peripheral leukocytes or from thyroid cancer tissues using QIAamp DNA Blood Kit or Trizol. Variants of polymorphisms were analyzed using TaqMan specific sonds on LightCycler 480. Statistical evaluation was performed by NCSS 2004 programme.
Results
Although total distributions of alleles of each gene were not different in patients compared to controls, the remarkable risk is in combination of specific alleles of these genes. G allele in TP53 in combination with T allele in CDKN1B is more often in patients with PTC than in controls (84.4 vs 74.7%, OR = 1.82; 95%CI (1.23–2.70); $P = 0.003$) and specifically the TT genotype in CDKN1B is the most risk in comparison with controls (70.8 vs 56.6%, OR = 1.86; 95%CI (1.18–2.94); $P = 0.01$). In MTC patients, C allele in TP53 with GG genotype in CDKN1B is more frequent compared to controls (6.2 vs 2.9%, OR = 2.2; 95%CI (1.19–4.08); $P = 0.016$).
Conclusion
It seems that genetic variants of tumor suppressor genes and mainly their cumulative risk effect play the role in the development of PTC and MTC. This work was supported by IGA MH CZ NT/13901-4 and MH CZ 00023761.

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P1102

Familial medullary thyroid carcinomas: RET mutation in exon 8 is associated with better prognosis but increased risk for other malignancies

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Objectives
In familial MTC there is genotype-phenotype correlation. The phenotype and clinical outcome in exon8 (G533C) carriers has not been well established.
Methods
95 patients operated for familial MTC (27.2% males) were followed for 0.9–30 years (mean 8.0, median 5.5 years). 45.3% ($n = 43$) were exon8 carriers (exon8MTC) and the remaning were non-exon8MTCs ($n = 52$, exons 10, 11, 13, 14, and 16). Pre-, postoperative calcitonin, extent of disease at diagnosis and at follow-up were recorded.
Results
Exon8MTC had significantly higher age at diagnosis even after when patients diagnosed after genetic-screening were excluded (43.0 ± 11 vs 27.9 ± 17, $P < 0.001$). Exon8MTC were diagnosed during 2001–2013 more frequently than before 2000 ($P = 0.001$). No difference in sex distribution was observed. No differences in lymph node invasion, capsular infiltration, multifocality, c-cell hyperplasia, and distant metastases at diagnosis were observed between groups. No difference in disease stage at diagnosis was observed between the two groups. When patients diagnosed after genetic-screening were excluded from analysis, stage at diagnosis was more favorable in exon8MTC compared to non-exon8MTC ($n = 51$, stage I+II: 60.9 vs 38.1%, stage III: 34.8 vs 33% stage IV: 4.3 vs 28.6%, $P = 0.037$, linear-by-linear association). Tumour size, preoperative and postoperative calcitonin levels did not differ between groups. Significantly more favorable clinical outcome was noted in the group of exon8MTC compared to non-exon8MTC (remission: 72.5 vs 52.2%, stable disease: 27.5 vs 30.4%, progression: 0.0 vs 17.6%, $P = 0.0037$). Interestingly, a higher percentage of exon8MTC patients carried a second malignancy either at diagnosis or at follow-up (21.4 vs 6.1%, $P = 0.058$).
Conclusions
Familial MTC due to exon8 ret mutation is frequently diagnosed in recent years in the Greek population. The age at diagnosis is higher in exon8MTC carriers compared to non-exon8MTC. The outcome of the disease is more favorable suggesting relatively slow disease progression. The higher prevalence of second malignancies has not been previously reported and merits further investigation.

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P1103

Single nucleotide polymorphisms associated with papillary thyroid cancer

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Papillary thyroid cancer (PTC) is well known family occurring cancer disease. It is estimated, that ~5% of differentiated thyroid cancers (where PTC is the most frequent) are hereditary. Susceptibility genes are poorly known, however, recently some SNPs located on chromosome 9 in FOXE1 locus (rs965513) and on chromosome 14 (rs944289) close to NKX2-1 locus have been confirmed to be associated with PTC in different populations.
The aim of our study was to analyze the association of four SNPs with PTC in Polish population. Analyzed SNPs were located on chromosome 9 in FOXE1 locus (rs965513, rs1867277, and rs1443434) and on chromosome 14 close to NKX2-1 locus (rs944289).
The whole material consisted of 2244 DNA samples from PTC patients and 1168 controls. rs965513 was analyzed in 833 cases and 845 controls, rs1867277 in 1724 cases and 869 controls, rs1443434 in 1779 cases and 788 controls, and rs944289 in all samples. SNPs were analyzed by allelic discrimination technique (7900HT Fast Real-Time PCR System, and Applied Biosystems).
We observed significant association of all investigated SNPs with PTC. OR values were significantly increased: for rs965513 OR was 1.43 (95% CI: 1.4–2.11, $P = 2.5 \times 10^{-7}$), for rs1867277 was 1.59 (95% CI: 1.33–1.89, $P = 3.4 \times 10^{-7}$), for rs1443434 was 1.53 (95% CI: 1.28–1.84, $P = 4.4 \times 10^{-6}$), and for rs944289 OR was 1.52 (95% CI: 1.26–1.83, $P = 9.6 \times 10^{-6}$).
Conclusion
All analyzed SNPs (rs965513, rs1867277, rs1443434, and rs944289) were significantly associated with papillary thyroid cancer in Polish population.

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P1104

A retrospective gender-comparative evaluation of differentiated thyroid cancers

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Background and aim
Differentiated thyroid cancers are the most common endocrine cancer types. They are more common in women, but the prognosis tends to be poorer with men. We aimed to evaluate male and female patients with differentiated thyroid cancer.
Subjects and methods
This retrospective study was performed in last 5 yearly hospital records of our hospital. All data about the patients' conditions were obtained from hospital information system (Probel) and we detected total 590 differentiated thyroid cancer (papillary and follicular) patients. Unfortunately four patients with a story of previously diagnosed metastatic malign cancer other than differentiated thyroid cancers and 128 patients with inadequate clinical data totally 132 patients were excluded from study and remained 458 patients were evaluated.
Statistical analysis
All results were presented as mean $\pm$ s.d. χ^2, Independent-Samples t-test, and Man–Whitney U-test' was used. $P < 0.05$ accepted as statistical significant.
Results
Majority of all patients were female (n:390, 85.2%). There were only 68 male patients (14.8%). Mean age at diagnosis of all patients was 49.8 ± 12.6 years and mean tumor size of all patients was 11.5 mm. Mean age at diagnosis (54.6 ± 13.6 and 48.9 ± 12.2 respectively, $P < 0.05$) and tumor size of male patients was higher than female patients 13.5 and 11.0 mm respectively ($P < 0.05$). Lymph node metastasis was detected in 40 patients (18.6%). Lymph node metastasis ratio of male patients (n:11) was higher than female patients (n:29) (respectively 16.1 and 7.4%, $P < 0.05$). Distant metastasis was detected in one male three female totally four patients ($P > 0.05$).
Conclusion
Differentiated thyroid cancers are common in females, but mean age at diagnosis, tumor size and lymph node metastasis ratio of male patients was higher than

female patients. There was no any significant difference in the other prognostic factors such as capsule invasion, multifocality, bilaterality, and distant metastasis.

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P1105

Nonincidentally and incidentally discovered thyroid cancer

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Introduction
Increasing incidence of thyroid cancer might be a consequence of an increase detection of subclinical disease. The aim of this study was to compare the clinical and pathologic characteristics of nonincidentally discovered (NID) thyroid cancer with incidentally discovered (ID) on postoperative pathology.
Methods
A retrospective medical record review of 104 patients with thyroid cancer was performed. A group I of 69 patients with NID thyroid cancer was compared with a group II of 35 patients with ID thyroid cancer.
Results
At diagnosis the mean age was 51.5 years for the group I and 56.1 years for the group II ($P=0.13$). The rate of male was 18.8% in the group I and 14.3% in the group II ($P=0.56$). Hashimoto's thyroiditis was present in 21.7 and 14.3% of patients in groups I and II respectively ($P=0.65$). Papillary tumor was the most frequent in both groups (87.0% in group I and 91.4% in group II). At TNM stage III and IV were present at a rate of 36.2 and 25.7% in the groups I and II respectively. There was no statistical difference in the mean size of tumor ($P=0.13$), focality ($P=0.61$), capsular involvement ($P=0.20$), and lymphovascular invasion ($P=0.33$). There weren't lymph nodes metastasis in group II compared with a rate of 11.6% in group I ($P=0.05$). Radioactive iodine treatment was most frequent in group I (68.1 vs 45.7%) $P=0.03$.
Conclusions
There weren't significant differences in the age, sex, presence of thyroiditis, size of tumor, focality, capsular, or lymphovascular invasion between the groups. There was an important rate of higher stage disease in the group II, nevertheless the ID thyroid cancer seems to be biologically less aggressive than NID, such as reported in other studies.

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P1106

The role of DNA repair proteins in the assessment of thyroid nodules

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Aims
Bening and malignant thyroid nodules are the most common lesions of endocrine glands. Some molecular markers; Mut-S homolog-2 (MSH2) and Mut-L-homolog-1 (MLH1) are the two of DNA repair proteins and metil guanin–DNA-metil transferase (MGMT) is the DNA repair enzymes have been studied. In this study, our aim is to evaluate MSH2, MLH1, and MGMT levels in papillary thyroid cancer (PTC), multinodular colloidal goitre (MNG), and chronic lymphocytic thyroiditis (CLT) and define as new diagnostic markers.
Materials and methods
Ninety patients' tissue specimens obtained from total or subtotal thyroidectomy materials with PTC ($n=29$; 50.07 ± 16.42 years), MNG ($n=26$; 52.96 ± 17.09 years), and CLT ($n=29$; 46.21 ± 11.80 years) were evaluated. The specimens were studied for MGMT, MSH2, and MLH1 immunohistochemically. Descriptive analysis, ANOVA test and Pearson's χ^2 test were used for statistical analysis.
Findings
Despite all MGMT, MLH1, and MSH2 were similar for follicular cell expression statistically, the staining was noticible in PTC group. The expressions for MGMT and MSH2 were similar for staining density and immunoreactivity within groups, but the expressions were more pronounced in PTC cells with nuclear and cytoplasmic staining. The groups were reevaluated for MSH2 follicular cell expression as $<50\%$ and $\geq50\%$. In this model CLT and MNG groups were different ($P=0.023$) and the difference was significant for staining density and immunreactivity ($P=0.001$ and $P=0.044$ respectively). Follicular cell expression between PTC and MNG ($P=0.032$), and immunoreactivity between CLT and MNG ($P=0.012$) were different for MLH1.
Results
Repair of DNA and the expression of its biomarkers are pronounced in malignant lesions. In this study, we found an increased expression of the three biomarkers MGMT, MLH1 and MSH2 in PTC compared to MNG as similar to CLT. Our result showing that these new biologic markers are useful differentiating benign and malignant lesions.

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P1107

Effects of zoledronic acid monohydrate on cytotoxicity and apoptosis in BCPAP human papillary thyroid carcinoma cell line

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Thyroid cancer in Turkey is the most common endocrine neoplasm with an incidence of 3.7%. Papillary thyroid carcinoma is the most common thyroid malignancy in a similar manner. Papillary thyroid carcinoma creates 50–90% of differentiated thyroid carcinomas. There is available in subgroups with poor prognosis. Case-specific mortality of 2% at 5, 10, and 20 years, only 4 and 5%. Mutations and re-arrangements in genes encoding proteins of the MAPK pathway for the development and progression of differentiated thyroid cancer, gain more, and more importance.
Bisphosphonates decrease tumor cell proliferation, reduce cell viability, stimulate apopitosis in tumor cell, inhibit cell adhesion and angiogenesis, and decrease metastatic potential *in vitro*.
We have established our hypothesis on the idea that this drug with minimal side effects has the potential to be an option instead of radioactive iodine treatment, or neoadjuvant prior to surgery or adjuvant therapy after surgery in patients with papillary thyroid carcinoma.
Zoledronic acid monohydrate with increasing doses of 10–100 μM was used on a papillary thyroid carcinoma cell line of human origin named BCPAP.
IC_{50} value with zoledronic acid monohydrate was found in first experiment at 48th h to be 55 μM, but second and third experiments failed. Therefore, apoptosis assays were not to be established. We investigate the reasons for inability to the result, and we will experiment again with a different papillary thyroid carcinoma cell line.

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P1108

Morphology of recurrent papillary thyroid carcinoma

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Background
Papillary thyroid carcinoma (PTC) is a well differentiated malignant tumour that usually has a good prognosis in vast majority of patients after thyroidectomy, suppressive hormonal, and radioiodine treatment. However 5–10% of PTC cases can develop local relapse and distant metastases.
Purpose of study
To make a comparative morphological analysis of PTC in two groups of patients: i) with and ii) without local relapse (regional metastases) after treatment.
Material and methods
H&E stained histological sections of primary PTC were reviewed in 17 cases of the group (a) and 18 cases of the group (b).
Results
Papillary architecture of the PTCs of group (a) was detected more often (58%) comparing with the group (b) (17%) ($P=0.0153$). Follicular and solid-follicular architectures were diagnosed more often in the group (b) (56%) comparing with the group (a) (12%) ($P=0.0116$). Focal tall, columnar, clear, and oxyphilic tumour cells were revealed more often in the group (a) (36%) comparing with the group (b) (5%) ($P=0.0408$).
Conclusion
Recurrent papillary thyroid carcinoma is characterized by predominantly papillary architecture of primary tumours with focal components of tall, columnar, clear, and oxyphilic tumour cells.

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P1109

Ca 19-9: is there a role for potential new biomarker for medullary thyroid cancer?

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In the recent years, knowledge about cancer biomarkers has increased tremendously providing great opportunities for improving the diagnosis, prognosis and treatment of cancer patients. In clinical practice, the levels of serum calcitonin, and carcinoembryonic antigen (CEA) are important during follow-up for patients with medullary thyroid cancer (MTC). Carbohydrate antigen 19-9 (CA 19-9), routinely used in the monitoring of pancreatic, hepatobiliary, and colon carcinoma, also has been detected in the tissue of ~ 6% of MTCs. However, its presence has never been reported in the serum of these patients.

We report seven cases of MTC presenting with elevated CA 19-9 serum levels (average level: 145 IU/l and normal range: <37 IU/l). All patients were Caucasians of European origin, (two males and five females; age range: 45–67 years), without any clinical findings of gastrointestinal cancer or inflammation. Additionally, the immunostaining of the MTC tissue showed positive result for calcitonin and CEA and strongly positive staining for CA 19-9.

The future of cancer management lie in the use of biomarkers that offer the potential to identify the cancer years before it is either visible or symptomatic. Exploring the presence of these markers that does not require the tumour tissue to detect them, but are secreted by cancer cells into the blood stream will not only facilitate easy detection, but will also be candidates for population based screening. A comprehensive understanding of the relevance of each biomarker will be important to efficiently diagnose the disease and provide appropriate strategies in the multiple therapeutic alternatives currently available that are likely to benefit to the cancer patients.

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P1110

Metastatic thyroid papillary microcarcinomas

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Aim

Thyroid papillary carcinomas smaller than 1 cm are called papillary microcarcinomas (PMC). They rarely metastasize to lymph node (LN) and distant areas. The presence of palpable lymphadenopathy at the time of diagnosis shows high risk of recurrence regardless of primary tumor size. We aimed to investigate histopathologic characteristics and recurrence frequency of thyroid PMCs with LN metastasis (LNM).

Materials and methods

Thyroid PMC cases with LNM that were followed by our department between 2009 and 2013 were evaluated retrospectively.

Result

There were eight patients (one male, seven females) and the average age was 41 years. The initial compliant was neck lump in four patients, three were already followed-up for thyroid nodule and one for parathyroid adenoma. All were undergone total thyroidectomy and neck dissection. All had received radioactive iodine treatment. None had a history for neck radiotherapy or thyroid carinoma in their family.

The tumor diameter was ≥5 mm in 75% of patients. The smallest one was 2 mm and the largest one was 9 mm in the diameter. Seven of eight patients had LNM at the time of diagnosis and the other had LNM during follow-up. 25% of patients had lymphovascular invasion, 37% had capsular invasion, and 50% had multifocality. None had extrathyroidal spread. 75% of patients had recurrence during follow-up. 83% of those patients had LNM at the time of diagnosis. 71% of the patients who had LNM at the time of diagnosis had recurrence (Table 1).

Conclusion

Thyroid PMCs generally have a good prognosis. They rarely show recurrence. However, the presence of LNM at the time of diagnosis is the most important factor for recurrence risk.

Table 1 Patients characteristics.

Patient	Age/ gender	Tumor size (mm)	LNM at the time of diagnosis	Follow-up (years)	Lympho-vascular/ capsular invasion	Multifocality/ number	Extra-thyroidal spread	Recurrence
1	26/F	9	+	1	+/−	+/many	−	+
2	35/F	2	+	1.5	−/−	+/2	−	+
3	38/F	7	−	9	−/−	−	−	+
4	53/M	6	+	4	+/+	−	−	+
5	55/F	8	+	8	−/+	−	−	−
6	41/F	3	+	0.5	−/−	−	−	−
7	40/F	8	+	1	−/−	+/3	−	+
8	43/F	9	+	2	−/+	+/4	−	+

+, yes; −, no.

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P1111

Prognostic implications of stage pT3 in well differentiated thyroid cancer

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Introduction

The TNM staging system for well differentiated thyroid cancer (WDTC) considers tumours over 4 cm diameter limited to the thyroid or tumours with minimal extra-thyroid extension to be classified as pT3. This stage can be considered quite heterogeneous, as different clinical and pathologic characteristics seem to have distinct prognosis value.

Aims

To determine prognostic factors amongst clinical, laboratorial, histologic and radiologic characteristics of WDTC pT3 patients followed in our department.

Materials and methods

A retrospective observational study of 129 patients with WDTC pT3 treated in our institution between January 2006 and December 2011 was performed. The following parameters were analysed: age, gender, personal and family history, histologic type, size, number of foci, presence of capsule, extra-thyroid extension, ^{131}I activity administered, post-^{131}I whole-body scintigraphy, using SPSS 21.0®. Patients were considered disease-free if there was no uptake outside the thyroid area in the post-dose scintigraphy, normal cervical ultrasound and stimulated thyroglobulin <2 ng/ml 9–15 months after initial treatment.

Results

Patients were followed for 48.2±16 months. At the end, 72.1% (n=93) patients were disease-free – group A, and 27.9% (n=36) had residual disease or relapse – group B. The size of primary tumour was significantly inferior in group A compared with group B (21.5±12.9 vs 30.6±20.8 cm; P=0.004), as the vascular invasion (36.4 vs 63.6%; P<0.001) and tumoral extension to adipose and fibromuscular tissue (38.5 vs 61.5%; P<0.001). In the post-^{131}I whole-body scintigraphy, the latero-cervical uptake was significantly less in group A (19 vs 81%; P<0.001). Mediastinic and distant metastasis were found only in group B (100 vs 0%; P<0.001). Thyroglobulin 3 months after surgery was significantly inferior in group A (0.3±0.3 vs 15±42.9; P=0.001). By logistic regression were identified as the most important independent factors predictive of cure: absence of latero-cervical uptake in post-^{131}I whole-body scintigraphy (OR=0.048; P<0.001) and tumour extension to adipose and fibromuscular tissues (OR=0.255; P=0.021).

Conclusions

In our cohort several clinical, pathological and radiological factors were associated with good prognosis (disease-free). In pT3 tumours, absence of node involvement and considerable extra-thyroid extension were the most relevant factors predictive of cure.

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P1112

The utility of ultrasonographic features on the accuracy of diagnosing individual types of thyroid malignancies

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Introduction
Recent studies have shown that different ultrasound features of a thyroid nodule are associated with high probability of different types of malignancy. The purpose of this study is to evaluate the sensitivities of each of the identified ultrasound features and to determine their corresponding carcinoma types that they are sensitive to.
Methods
Retrospective data from January 2010 to October 2013 were collected in a regional thyroid unit in the UK. Patients who had a histological diagnosis of thyroid malignancy were included in the study. Their scan reports and histological reports were obtained and analysed.
Results
100 patients were histologically diagnosed with thyroid malignancy. Five recurrent ultrasound characteristics were identified from the reports of these patients: microcalcification (19%), hypoechogenicity (32%), intranodular-vascularity (34%), irregularity (15%) and halo-like (5%). Their types of malignancy were papillary (63%), follicular (23%), medullary (3%) and Hürthle cell (7%) carcinomas. However, none of the ultrasound features was particularly sensitive to any of the carcinoma types, i.e. papillary and follicular carcinomas had similar sensitivities to individual ultrasound features; medullary and Hurthle cell carcinomas were too few to be considered statistically significant.
Conclusions
We conclude that there is no single ultrasound feature or combination of features having a high sensitivity to individual types of thyroid malignancy.
The limitations of this study are: i) some ultrasound features of the thyroid nodules might have been omitted; ii) some patients did not have ultrasound scan and histology reported; and iii) the sample size restricted the evaluation of all carcinoma types. Further work is required to standardise the implementation and reporting of thyroid ultrasound scan to allow continuous practice evaluation and provision of effective management of thyroid nodules.

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P1113

Prognosis of papillary and follicular thyroid cancers with serum thyroglobulin antibody at 1 year after total thyroidectomy

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Objective
To investigate the influence of serum TgAb on the therapeutic outcome in papillary and follicular thyroid cancer patients.
Methods
In 1378 papillary and follicular thyroid cancer patients (women, 1055 and men, 323; mean age, 42.5 years) with T2 and higher, or N1, or M1 classifications in TNM staging who had undergone total thyroidectomy, we recorded the serum TgAb data (on thyroxin therapy) 1 year ($\pm$3 months) after thyroidectomy. The patients were classified as negative TgAb or positive TgAb on the basis of their serum TgAb levels 1 year after surgery (<50 or ≥ 50 IU/mL).
Results
Among the 1378 patients, 77 were with positive TgAb and 1301 were with negative TgAb. The median follow-up duration was 11.7 years (range, 2–27.2 years). The patients with positive TgAb had comparable prognosis to the patients with negative TgAb (22.1% cancer recurrence vs 21.1% cancer recurrence, $P=0.845$; 9.1% cancer mortality vs 7.8% cancer mortality, $P=0.693$). By the multivariate analyses, there is no significant difference in the prognosis between positive TgAb patients and negative TgAb patients (cancer recurrence, $P=0.150$ and cancer mortality, $P=0.306$).
Conclusion
Positive serum TgAb 1 year after total thyroidectomy may not influence the prognosis of papillary and follicular thyroid cancer patients in the study.

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P1114

Increased mean platelet volume in papillary thyroid cancer

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Introduction and objective
Platelets play an important role in the development of thrombotic events. Increase of mean platelet volume (MPV) may indicate pre-thrombotic conditions as a new cardiovascular marker. Larger platelets have been reported to be metabolically more active than smaller ones. Our aim of present study is to evaluate MPV levels in patients with papillary thyroid cancer.
Materials and methods
Forty-seven patients with newly diagnosis more advanced papillary cancer, 47 micropapillary cancer who referred our Endocrinology Department and 62 age- and BMI-matched healthy subjects were included in the study. All the study subjects were evaluated by biochemical and platelet parameters. All complete blood count (CBC) analysis was performed with the automatic hematology analyzer Beckman Coulter LH 750 (Beckman Coulter, USA) in euthyroid state and preoperative period. All hormonal analyses were done by chemiluminesance assay. All statistical analysis was performed retrospectively.
Results
Mean age were 43.53 ± 10.94 years in micropapillary cancer; 43.26 ± 13.24 years in more advanced papillary cancer; 37.64 ± 15.07 years in control subjects. Mean BMI were 27.84 ± 5.3 kg/m^2 in micropapillary cancer; 28.32 ± 4.32 kg/m^2 in more advanced papillary cancer; and 25.16 ± 6.32 kg/m^2 in control subjects. Tumor diameters at the time of diagnosis were 0.4 ± 0.27 cm in micropapillary cancer and 2.54 ± 1.27 cm in more advanced papillary cancer. Serum MPV levels in both of papillary cancer groups were significantly different from control subjects (8.75 ± 1.13 fl in micropapillary cancer; 8.75 ± 1.13 fl in more advanced papillary cancer; 7.88 ± 0.8 fl in control ($P=0.000$, $P=0.000$, and $P=0.000$ respectively). To assess the correlation with MPV, a Pearsons correlation analysis was performed on each variable. MPV had a positive correlation between serum thyroglobuline levels ($r=0.24$, $P=0.04$), tumor diameters ($r=0.265$, $P=0.03$) and age ($r=0.213$, $P=0.015$). The multiple regression analysis of MPV and other risk factors was performed. Age, gender, and BMI were independent predictive factors of MPV.
Conclusions
The high MPV levels in papillary thyroid cancer may increase cardiovascular risk or thrombotic events. There is a need for further prospective study which was clarifiedrelationship between papillary thyroid cancer and prognostic value of high MPV levels.

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P1115

Preoperative TSH value, does it predict the surgical findings in papillary thyroid cancer?

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TSH level has been proposed as a thyroid malignancy predictor in nodular thyroid disease. In addition, several clinical studies have reported that higher preoperative serum TSH levels were associated with more advanced stages of differentiated thyroid cancer (DTC) at the time of diagnosis.
Methods
We collected retrospectively preoperative serum TSH from patients diagnosed of papillary thyroid cancer (PTC) who had undergone total thyroidectomy during the period 2001–2013 in a single tertiary center. We recorded demographic data, nodule number, tumor size and neoplasm features in surgical pathology. Patients with Graves's disease or primary hypothyroidism under treatment prior to surgery were excluded.
Results
A total of 348 patients were included: 92 with incidental microcarcinoma (IMC), 54 with non-IMC (NIMC) and 202 with PTC larger than 1 cm, 105 of them larger than 2 cm. There were no significant differences in TSH levels among IMC and non-incidental cases (2.13 vs 2.53 IMC; *P*: 0.12). Likewise, TSH concentration was similar in NIMC, PTC >1 and PTC >2 cm (2.85; 2.45 and 2.31 respectively). Neither the presence of multifocality (2.62 vs 2.32), nor

extrathyroidal extension (2.78 vs 2.33), nor lymphatic invasion (2.78 vs 2.4) were associated with TSH levels, although higher TSH levels where found when one of those features was present. Aggressive cellular variant or vascular invasion showed lower levels of preoperative TSH (2.17 vs 2.48; *P*: 0.43). Only the presence of antimicrosomal Abs or diffuse lymphocytic infiltration was significantly associated with higher TSH level. These results did not change when considering exclusively uninodular non-incidental disease in the analysis, although almost all the parameters had lower *P* value.

Conclusions

Our series suggests that high TSH levels may be involved in the presence of pathological characteristics associated with worse outcome in PTC, but with no statistical significance, unlike to other published series. The only feature actually associated to higher TSH was the presence of autoimmunity.

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P1116

Thyroglobulin measurements in fine-needle aspiration cytology of lymph nodes in patients after thyroidectomy because of differentiated thyroid cancer

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Introduction

Approximately 5–20% patients treated for differentiated thyroid carcinoma (DTC) develop metastases to the neck lymph nodes. Ultrasound-guided fine-needle aspiration biopsy (FNAB) is a routinely used method in the examination of suspicious lymph nodes. The measurement of thyroglobulin (Tg) levels in needle washout fluids (FNAB-Tg) has been reported to increase the diagnostic accuracy of FNAB.

Description of methods/designs

A total of 101 patients with lymphadenopathies who underwent surgery because of DTC were included in analysis. Ultrasound-guided FNAB and FNAB-Tg measurements of suspected lymph nodes were performed. FNAB-Tg levels were established by electrochemiluminescence (ECLIA). Results of microscopic examinations of FNAB smears and corresponding FNAB-Tg values were compared to the histology of removed lymph nodes and/or to clinical follow-up.

Results

All patients with positive cytology underwent surgery ($n=19$). Patients with elevated levels of FNAB-Tg and negative cytology underwent surgery ($n=1$), were treated with ^{131}I ($n=2$) or were observed ($n=1$). In 19 of 21 patients with elevated levels of FNAB-Tg FNAB disclosed carcinoma cells. In the remaining two cases FNAB was not diagnostic. In five patients with positive cytology, FNAB-Tg levels were not elevated. Three of these patients presented with cervical lymphadenopathy shortly after thyroidectomy and two had cervical metastases from other malignancies.

Conclusions

Ultrasound-guided FNAB is not sensitive enough to detect all metastatic lymph nodes. FNAB-Tg measurement is an valuable adjunct to the cytological examination of suspicious neck lymph nodes, increasing its diagnostic accuracy. FNAB-Tg should be recommended for the management of metastatic lymphadenopathies in the follow-up of patients with DTC, particularly in difficult cases such as detecting of small and cystic metastases and in cases of indeterminate cytology.

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P1117

Prediction of lymph node metastasis in papillary thyroid cancer by preoperative BRAF analysis, is it useful?

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Introduction and objective

Prophylactic central lymph node dissection (CLND) in patients with suspected papillary thyroid cancer (PTC) without evident lymph node metastasis (LNM), remains debatable. We propose to evaluate whether BRAF V600E mutation presence, could help to identify patients at risk for LMN.

Methods

Retrospective study of patients with diagnosis of PTC, who underwent total thyroidectomy during 2002 and 2013 (*n*: 256) in our hospital. Patients with pathological diagnosis of PTC, whose BRAF V600E mutation status was known (*n*: 170) and who underwent lymphadenectomy (*n*: 118) as well, were selected. LMN presence was correlated with BRAF V600E mutation status (presence of BRAF V600E mutation vs WT) and with other clinicopathological factors (age, initial tumor size, gender, etc.). A multivariate analysis was performed to assess independent factors related to LNM. DNA was extracted from paraffin-embebbed tissues section and V600E mutations were detected by HRM followed by sequencing confirmation.

Results

From 118 PTC studied, 74.6% were women with an age at diagnosis of 44.8 ± 15.4 years. The prevalence of the V600E mutation was 62.7%. 60.2% of patients had LNM, in which 57.7% were BRAF V600E mutation carriers and 43.3% were WT ($P=0.170$, NS). We did not find association with other clinicopathological factors, except with extrathyroidal affectation and male gender, which were associated with higher prevalence of LNM ($P<0.05$). In the multivariate analysis, the only independent factor associated with LMN was extrathyroidal affectation (OR: 3.0 95% CI: 1.8–7.9, $P<0,05$).

Conclusions

Our results do not support using the presence of V600E mutation to decide whether to perform or not prophylactic CLND in patients with PTC. More prospective studies will be necessary.

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P1118

Clinical and biochemical characteristics of papillary thyroid cancer according to the presence of BRAF (V600E) mutation

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Introduction

BRAF (V600E) mutation is the most frequent detected genetic change in papillary thyroid cancer (PTC). Its presence has been related to aggressive clinical and pathological features. Therefore, BRAF mutation has drawn considerable interest as a potential prognostic factor for PTC. The presence of the mutation confers the tumour a disability to uptake RAI, diminishing the therapeutic tools. However if this feature is related to some kind of tumour dedifferentiation is not known. The aim of this study was to explore if there were any differences in preoperative thyroglobulin (PTg) levels and the presence of autoimmunity (PTg Ab), among patients harbouring the mutation and those who did not.

Methods

We evaluated 62 patients (51 females) with pathological diagnosis of PTC. All of them underwent total thyroidectomy, 55 central lymph node dissection, and 13 lateral neck dissection as well. DNA was extracted from neoplastic cells and BRAF mutation was detected by PCR and sequencing. Analysis included age, preoperatively TSH, PTg and PTg Ab, tumour size and thyroid weight.

Results

The prevalence of the BRAF mutation (BRAF+) in our patients was 51.6%.
According to sex, 45.5% males and 53% females were BRAF+ ($P=0.68$).
Mean age was 48.9 years in BRAF+ vs 50.4 in BRAF− ($P=0.71$).
Mean tumour size was 16.8 mm in BRAF+ vs19.4 in BRAF− ($P=0.43$).
Median thyroid weight was 23 g in BRAF− and 19.5 g in BRAF+ ($P=0.31$).
Mean TSH level was 2.33 μ/l in BRAF− vs 3.26 in BRAF+ ($P=0.14$).
PTg level was 355.6 ng/mL in BRAF− vs 154.5 ng/mL in BRAF+ ($P=0.13$).
PTg Ab were positive in 29.6% in BRAF− vs 33.3% in BRAF+ patients ($P=0.6$).

Conclusions

In our series, harbouring BRAF mutation, neither implies less production of Tg by the tumour, nor higher frequency of autoimmunity, although there is a tendency towards less PTg concentration and smaller tumour size. Nevertheless higher PTg levels may be related to a trend to heavier thyroid gland. In view of these results, and considering the small size of the sample, we cannot conclude that the presence of BRAF mutation, involves any grade of dedifferentiation in PTC.

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P1119

Survivin splice variants expression in thyroid malignancy

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Introduction
Thyroid cancer incidence has increased significantly during the past decades and is the most common type of endocrine malignancy. Suitable criteria for detecting malignant thyroid tumors are still missing. Therefore, the discovery of molecular markers linked to thyroid carcinogenesis will be helpful in the diagnosis of malignant tumors and managing their appropriate treatment.
Aim
The objective of the study was to evaluate survivin expression and its splice variants: survivin delta Ex3 and survivin 2B in benign and malignant thyroid nodules.
Methods
Thyroid tissues samples were collected from 50 patients: 29 patients with thyroid cancers including medullary, papillary, follicular and undifferentiated ones, as well as form 21 patients with benign thyroid lesions.The analysis of the survivin gene expression profile and the level of the splice variants of the gene was performed using quantitative RT-PCR.
Results
A significantly higher expression of survivin gene ($P=0.0232$) was detected in thyroid malignant nodules, as compared with benign lesions. The highest expression rate was noted for the survivin delta Ex3 splice variant in different types of thyroid carcinomas ($P=0.0009$). Moreover, the comparison of relative survivin expression in tumors staged pT1 and pT3 or pT4 revealed a much higher expression in tumor tissues of pT3/pT4 ($P=0.0052$). Additionally the expression of survivin in undifferentiated thyroid carcinomas was higher than in differentiated ones ($P=0.0095$).
Conclusion
The results suggest that survivin expression may be an indicator of the thyroid malignancy.

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P1120

Diffuse sclerosing variant of papillary thyroid carcinoma is a rare variant

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Diffuse sclerosing variant of papillary thyroid carcinoma is a rare variant. It is usually seen in children and young adults.The thyroid gland is diffusely involved. It is characterized by scattered microscopic tumor islands, diffuse fibrosis, calcification, abundant lymphocytic infiltration and psammom body when compared with conventional papillary thyroid carcinoma. Usually the lesion does not cause mass but rather a dominant nodule in one lobe is present in 50% of cases. Lymph node metastasis is found in nearly all of the cases and distant metastasis is often present.Although the prognosis is not good, it responds to treatment.
Case
A 18-year-old female patient with Hashimoto's thyroiditis applied to the Numune State Hospital for enlargement in right thyroid gland. Thyroid ultrasound showed nothing except roughness and heterogeneous appearance in the thyroid. The patient was called to follow-up visits. As the patient felt further enlargement in the thyroid, a repeat USG was performed which showed a heterogenous appearance with microcalcifications. Thyroidal fine needle aspiration was done for exclusion of thyroidal lymphoma. The smear showed hurthle cells having prominent nucleoli and pleomorphic nuclei with highly atypical features on the ground of chronic inflammatory cells. The cells were forming papillary structures in three-dimensional pattern. Total thyroidectomy and cervical lymph node dissection was done to the patient. She was reported as 'Thyroidal papillary carcinoma, diffuse sclerosing variant' after pathological examination.
Discussion
Diffuse sclerosing variant is a rare variant of papillary thyroid carcinoma. It is characterized histopathologically by psammom bodies, papillary structures within lymphovascular structures, squamous metaplasia, stromal fibrosis and dense lymphoid infiltration.
A 18-year-old female patient having a rare variant of papillary carcinoma who applied with complaints of enlargement in thyroid and was diagnosed by blind biopsy not from a nodule is discussed in this report.

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P1121

The role of microRNAs in regulation of RARβ and its function in development of papillary thyroid carcinoma

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Objectives
Papillary thyroid carcinoma (PTC) exhibits aberrant expression of retinoic acid receptor β (RARβ), a retinoic acid-inducible transcription factor, essential for cellular growth and development. The mechanisms leading to decreased RARβ expression in tumors are unknown. We hypothesized that changes in expression of *RARB*, a gene encoding for RARβ, result from aberrant expression of microRNAs. We elucidated the miRNome of normal thyroid and PTC by microarray and next-generation sequencing experiments (NGS) and identified microRNAs highly upregulated in cancer. The list included miR-146a and miR-146b, putative regulators of *RARB*.
Aim of the study
Aim of the study was to analyze the action of miR-146a and miR-146b on RARβ expression in PTC and its role in development and progression of cancer.
Methods and results
NGS and real-time PCR analysis performed in 30 PTC and match-control tissue samples recognized miR-146a and miR-146b as highly upregulated in PTC. *In silico* analysis identified *RARB* as a target for both microRNAs. Q13-PCR analysis of *RARB* expression showed its downregulation by 65% ($P=0.00001$) in PTC. Direct interaction between miRNAs and *RARB* was tested by luciferase assay using a reporter vector, containing *RARB* 3′UTR cloned downstream of luciferase gene. MicroRNA-146a caused a 37% ($P=0.00001$) and microRNA-146b a 15% ($P=0.0001$) reduction of luciferase expression. Impact of miR-146a and miR-146b on *RARB* was further confirmed in cell line by showing a 28% ($P=0.002$) and 27% ($P=0.006$) decrease of endogenous *RARB* expression respectively.
Conclusion
This is the first study showing microRNA-dependent regulation of *RARB* expression. Lowered levels of *RARB*, underlying tumorigenic changes in thyroid gland, may be a result of upregulation of miR-146a and miR-146b observed in PTC. Since disturbances in microRNA expression are reversal, modulating the expression of miR-146a and miR-146b can facilitate future gene therapies in cancers that are resistant to retinoic acid treatment.

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P1122

Rising serum thyroglobulin in the follow-up of patients with differentiated thyroid carcinoma: the role of FDG PET–CT

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Rising thyroglobulin (Tg) serum concentration in patients after total thyroidectomy due to differentiated thyroid cancer (DTC) with no pathological radioiodine uptake on posttherapeutic whole-body scan (WBS) constitutes a challenge for physicians dealing with DTC management.

The FDG PET–CT is regarded as a gold diagnostic standard in such cases.
Our aim was to find factors which may help predicting positive PET–CT result, and to evaluate its impact on management decisions.
The study was a retrospective analysis of the results of PET–CT performed in a group of 71 DTC patients. Positive PET–CT result was obtained in 35 cases. PET (+) group showed to differ significantly in many aspects, as age, the most common cancer type and medical history, from the PET (−) one. The PET–CT results were positive in cases of long-term radioiodine treated patients in whom significant Tg rise had been observed, as well as in cases of never-iodine avid metastases. In PET (+) group mean Tg concentration was significantly higher than in PET (−) group (721.6 ng/ml vs 62.2 ng/ml) and Tg 2-year increase was on av. 236.2% in PET (+) while 70.5% in PET (−) group (in endogenous TSH stimulation).
In PET (+) group metastases to neck lymph nodes or neck soft tissues were found in 11 cases, pulmonary metastases in 14 cases, mediastinal lymph nodes were affected in nine cases, one case of liver metastasis and six cases of bone metastases were found. Surgery treatment was offered to ten patients, radiotherapy to six patients, and five patients entered treatment programs with thyrosine kinase inhibitors. Other patients remain in active observation.
Conclusion
PET–CT is a useful diagnostic tool which brings important information with an impact on further treatment of properly selected DTC patients.

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P1123

Sodium–iodide symporter and its microRNA-dependent deregulation in papillary thyroid carcinoma.

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Objectives
The sodium/iodide symporter (NIS) is a glycoprotein with unique ability of transporting iodine into the thyroid follicle. Apart from the importance in thyroid hormone synthesis, this function of NIS allows the use of radioactive iodine to target residual and metastatic thyroid cancer after thyroidectomy. However, 20–30% of thyroid tumors exhibit lowered expression of NIS, resulting in decreased uptake of radioiodine and inefficient post-surgical therapy. Mechanisms leading to downregulation of NIS are unknown. We hypothesize that this phenomenon results from upregulation of microRNAs, non-coding regulators of gene expression.
Aim
The aim of this study was to identify microRNAs that regulate the expression of NIS and contribute to its deregulation in papillary thyroid carcinoma (PTC).
Methods and results
In silico analysis identified microRNAs putatively binding and regulating NIS. Direct interaction between identified microRNAs and NIS was determined in luciferase assay, in cell lines transfected with synthetic microRNAs and a reporter plasmid with 3′UTR of NIS cloned downstream of luciferase. Significant reduction of luciferase activity was demonstrated for miR-146b-3p (34%, $P=0.028$), miR-146b-5p (25%, $P=0.006$), miR-339-5p (21%, $P=0.006$) and miR-129-2-3p (29%, $P=0.004$). Real-time PCR performed in 48 pairs of PTC and control, non-cancerous tissue showed a 20-fold decrease of NIS in cancer ($P=8\times10^{-7}$) together with a 80-fold increase of miR-146b-3p ($P=3.3\times10^{-8}$) and 140-fold increase of miR-146b-5p ($P=2.1\times10^{-8}$). Furthermore, NIS levels were negatively correlated with levels of miR-146b-3p ($r=-0{,}40, P=0.01$) and miR-146-5p ($r=-0.47$, $P=0.002$). Further clinicopathological analysis revealed negative correlation between NIS expression and tumor size ($r=-0.32$, $P=0.026$).
Conclusions
This is the first study showing the role of microRNAs in regulation of NIS expression. We propose that downregulation of NIS in PTC results from elevated levels of microRNAs. Since overexpression of miRs is reversal, inhibition of identified microRNAs may result in restoration of NIS expression and reestablishment of radioiodine uptake by thyroid cells.

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P1124

Functional analysis of newly discovered microRNA deregulated in papillary thyroid carcinoma

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Introduction
Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy where alterations in the RET/PTC–RAS–BRAF signaling pathway and deregulation of microRNA (miRNA) expression are suggested to be major mechanism of pathogenesis. MicroRNAs are small non-coding RNA molecules that recognize specific sequences in 3′UTR of target gene and prevent from its translation. Our recent deep sequencing studies of thyroid tissue transcriptome revealed a putative novel small non-coding RNA, encoded within *PAX8* gene. *In silico* analysis confirmed that the short non-coding sequence could be miRNA. We aimed to investigate the role of newly identified microRNA (miR-PAX8) in thyroid carcinogenesis.
Methods and results
To confirm functionality of newly discovered RNA, pcDNA3 vector expressing pri-miRNA was transfected into U2-OS cells. TaqMan assay confirmed the proper processing towards mature miRNA in transfected cells. Analysis of *PAX8* mRNA and miR-PAX8 expression in 42 pairs of PTC and matched control tissue showed 28% ($P=0.02$) decrease of miR-PAX8 and 40% ($P=0.001$) decrease of *PAX8* mRNA in tumor compared with noncancerous tissue (correlation $r=0.57$, $P=0.00008$). Using *in silico* analysis we chose *CTBP1* gene as a target gene of miR-PAX8 for further studies. qPCR analysis revealed 1.6-fold ($P=0.001$) increase of *CTBP1* mRNA in PTC compared to control tissue that could potentially results from miR-PAX8 decrease (correlation $r=-0.45$, $P=0.002$). Direct interaction of miR-PAX8 with *CTBP1* transcript was confirmed by luciferase assay using vector with *CTBP1* 3′UTR cloned downstream to luciferase. Cells transfected with pGL3-3′UTR construct and vector expressing pre-miRNA revealed 17% ($P=0.002$) decrease in luciferase expression.
Conclusions
We demonstrated that the newly discovered non-coding RNA is functional microRNA that is downregulated in PTC tissue. As CTBP1 mediates repression of several tumor suppressors, interaction of miR-PAX8 with *CTBP1* transcript suggests that novel miRNA could be involved in PTC development. To strengthen this hypothesis further studies including Western blot and flow cytometry analysis will be performed.

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P1125

Apical iodide transporter and its microRNA-induced silencing in thyroid malignancies

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Objectives
Apical iodide transporter (AIT) is essential for thyroid homeostasis, functioning both as iodide transporter and a potent tumor suppressor. Its decreased levels observed in thyroid cancer underlie its progression and inefficiency of radioactive iodine treatment, used for ablation of post-operative and metastatic thyroid cancer cells. Mechanisms of AIT downregulation in cancer are largely unknown, but recent data on overexpression of microRNAs in thyroid cancer suggested their possible role in deregulation of AIT.

Aim of the study
The aim of this study was to establish the impact of microRNAs on regulation of AIT expression and to assess the role of deregulation of this process in thyroid carcinogenesis.
Methods and results
MicroRNAs targeting AIT were identified *in silico* and their interaction with AIT was confirmed in luciferase assay. Significant reduction of luciferase activity was obtained for miR-181a-5p (down 20%, $P=0.02$), miR-182-5p (18%, $P=0.05$), and miR-494-3p (15%, $P=0.01$), indicating binding of these microRNAs to 3′UTR of AIT. Q17-PCR analysis in 48 PTC and non-tumorous paired tissue samples revealed a 67-fold decrease of AIT ($P=2\times10^{-7}$) in PTC and a concomitant upregulation of miR-181a-5p (1.67-fold, $P=0.001$) and miR-182-5p (2.03-fold, $P=0.002$). AIT expression was additionally 4.79-fold lowered ($P=0.001$) in presence of BRAFV600F mutation. AIT levels negatively correlated with tumor size ($r=-0.29$, $P=0.03$, $n=54$). Q17-PCR analysis of 19 thyroid adenomas showed a 2.24-fold decrease of AIT, accompanied by upregulation of miR-181a-5p (1.8-fold, $P=0.02$), miR-182-5p (5.4-fold, $P=0.05$), and miR-494-3p (6.1-fold, $P=0.01$). Downregulation of AIT was correlated with upregulation of its downstream effector, antiapoptotic survivin ($r=-0.45$, $P=0.055$).
Conclusions
This is the first study showing microRNA-dependent regulation of AIT expression and its aberrances in thyroid malignancies. Modulating the levels of miR-181a-5p, miR-182-5p, and miR-494-3p could be used for restoration of AIT and reversal of carcinogenic process, as well as to reestablishment of radioiodine uptake by thyroid cells.

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P1126

TERT promoter mutations correlate with a more advanced stage at diagnosis and with a poorer prognosis in differentiated thyroid cancer

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Telomerase is a ribonucleoprotein polymerase that maintains telomere ends and plays a role in cellular senescence, being repressed in postnatal somatic cells. Mutations C228T and C250T of the telomerase reverse transcriptase (TERT) were recently reported in human cancers. In thyroid cancer, TERT mutations are more frequent in aggressive histotypes, but very few data are available about the potential correlations with clinical features in papillary and follicular thyroid cancers (PTC and FTC). In the present study, TERT proximal promoter mutations were explored in a large series of 182 PTCs and 58 FTCs and correlated with clinical and prognostic data. TERT mutations were found in 22/182 (12%) PTCs and in 8/58 (14%) FTCs, being TERT C228T the most prevalent. No mutations were found in 20 controls. TERT mutations were significantly associated with an older age at diagnosis and a worst outcome and they were the only significant independent predictors of persistence/recurrence ($P=0.0002$ at logistic regression analysis). $BRAF^{V600E}$ mutation was found in 64/182 tumors (35.2%). $BRAF^{V600E}$ tumors harbored more frequently a TERT mutation than $BRAF^{WT}$ cases (15.6 vs 10.2%). In FTCs, *ras* mutations were found in 14/58 cases. The prevalence of TERT mutations in ras^{mut} and ras^{WT} cases was of 14.3 and 13.6% respectively. Seven metastatic lymph-nodes were also studied and their molecular pattern was identical to that of the primary tumor in 4, while it was discrepant in three patients (acquirement or loss of a TERT or BRAF mutation in the metastasis).
In conclusion, we found a 13% prevalence of TERT mutations in a large series of differentiated thyroid cancers. TERT mutations were the only significant independent predictors of persistence/recurrence and seem to be strong markers of tumor aggressiveness, allowing to identify the small subgroup of tumors with a poorer outcome and for those a more aggressive treatment should be deserved.

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P1127

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Hashimoto's thyroiditis (HT) is found in a high proportion of resected thyroid specimens. There has been considerable controversy as to whether having HT predisposes a patient to papillary thyroid cancer (PTC) and conflicting data have been reported with regard to HT and risk of malignancy. The aim of this study was to evaluate coexistence of PTC with HT.
Materials and methods
This is a retrospective study done at American Hospital 2 from April 2011 until December 2013. We analyzed the data from 71 patients who underwent thyroid surgery at our institution. Of these, 29 patients were diagnosed with PTC. All patients diagnosed with PTC were evaluated for the presence of HT by measuring thyroid autoantibodies. If a patient had at least one positive thyroid autoantibody, then the patient was defined as having HT.
Results
From a total of 71 patients who underwent thyroid surgery there were 29 patients diagnosed with PTC three males (10.3%) and 26 females (89.7%), mean age 41.9 (age 18–73) years old. Thyroid antibodies ac anti-TPO and ac anti-thyroglobulin were measured in all patients with PTC. They were positive in six patients with PTC (20.6.8%). They were all female patients.
Conclusion
These data demonstrate that HT is associated with an increased risk of developing PTC. We also observed a high ratio of females diagnosed with PTC compared with males. An adequate follow up of patients with HT may permit an early diagnosis of differentiated thyroid cancer and its appropriate management. More prospective studies with longer follow-up are needed to further elucidate this relationship. Thus, more aggressive surveillance for PTC may be indicated in patients with HT, especially in women.

Keywords
Hashimoto's thyroiditis; papillary thyroid cancer; antibody.
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P1128

Next-generation sequencing reveals a novel thyroglobulin-embedded microRNA gene deregulated in papillary thyroid carcinoma

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Introduction
Papillary Thyroid Carcinoma (PTC) exhibits activation of MAPK (Mitogen-activated protein kinases) pathway, leading to uncontrolled cellular division and growth. Concomitantly, thyroid tumors exhibit aberrant expression of numerous microRNAs, which are non-coding RNAs that inhibit expression of protein-coding genes. Employing next-generation sequencing (NGS), we revealed comprehensive miRNA profiles of normal thyroid and PTC, and identified putative novel microRNA genes.
Aim
The aim of this study was to analyze the role of the novel microRNA in physiology and neoplastic transformation of the thyroid gland.
Methods and results
NGS analysis performed in 14 PTC and control samples resulted in identification of a novel microRNA encoded within the thyroglobulin gene (TG), important regulator of thyroid homeostasis. Cloning into the expression vector, cell line transfection and Taqman quantification revealed that the microRNA gene was processed towards mature microRNA. Q20-PCR analysis in 33 PTC and matched non-tumorous tissue samples showed that the levels of miR-TG and thyroglobulin were decreased in tumor by 30% ($P=0.001$) and 16% ($P=0.04$), respectively. Levels of both transcripts were positively correlated ($r=0.48$, $P=0.005$). In silico analysis revealed that genes putatively regulated by novel microRNA included MAPK and Pi3K/Akt pathway proteins: DUSP6 and MAP4K4. Q20-PCR showed a 12-fold upregulation of DUSP6 ($P=0.00001$) and a 2.5-fold upregulation of MAP4K4 ($P=0.002$) in PTC compared to control tissue. Moreover, expression of both genes negatively correlated with expression of novel microRNA: $r=-0{,}44$ for DUSP6 ($P=0.01$) and $r=-0.48$ for

MAP4K4 ($P=0.005$). Direct binding of studied microRNA to 3'UTRs of MAP4K4 and DUSP6 was confirmed in luciferase assay, leading to reduced luciferase activity by 10% ($P=0.0006$) and 17% ($P=0.0008$), respectively.
Conclusion
We propose that the novel microRNA encoded within TG fine-tunes the MAPK pathway, inhibiting expression of DUSP6 and MAP4K4. Severe downregulation of the microRNA leads to activation of MAPK kinases, underlying initiation and progression of thyroid carcinogenesis.

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P1129

The role of *ATM–CHEK2–BRCA1* axis in determination of genetic predisposition and clinical presentation of papillary thyroid carcinoma

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Background
Risk of developing papillary thyroid carcinoma (PTC), the most frequent thyroid malignancy, is elevated up to 8.6-fold in the first-degree relatives of PTC patients, what could be explained by polygenic action of low-penetrance alleles. Since the DNA-damaging exposure to ionizing radiation is a known risk factor for thyroid cancer, polymorphisms in DNA repair genes are likely to affect this risk. Among the DNA repair proteins, the ATM–CHEK2–BRCA1 axis seems to be of particular interest. In response to double-strand DNA breaks, ATM is recruited to DNA damage sites, phosphorylating BRCA1 and CHEK2 and initiating a signalling cascade of DNA damage response and cell-cycle control proteins.
Aim of the study
The aim of this study was to identify low-penetrance susceptibility alleles for PTC by genotyping deleterious SNPs in genes involved in DNA damage-response and cell-cycle pathways.
Methods and results
Sequenom iPLEX technology was employed to genotype polymorphisms: rs1801516 in ataxia telangiectasia mutated (*ATM*), rs17879961 in CHEK2 checkpoint yeast homolog (*CHEK2*), and rs16941 in breast cancer 1 gene (*BRCA1*) in 1781 PTC patients and 2081 healthy controls. We identified *BRCA1* rs16941 (odds ratio (OR)$=1.16$, $P=0.005$) and *CHEK2* rs17879961 (OR$=2.2$, $P=2.37\times10^{-10}$) as the risk alleles for PTC. *ATM* rs1801516 variant modifies the risk associated with *BRCA1* variant by 0.78 ($P=0.02$). Both *ATM* and *BRCA1* variants modify the impact of male gender on clinical variables: T status ($P=0.007$), N status ($P=0.05$), and stage ($P=0.035$).
Conclusion
This is the first study showing the complex association between genetic variants of ATM–CHEK2–BRCA1 axis and the predisposition to PTC. The study supports previous findings on the importance of age and gender on the clinical outcome of the disease and showed that this effect is significantly altered by the minor alleles of the analysed genes, emphasizing their importance in the pathogenesis of PTC.

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P1130

Evaluation of factors predict the efficacy of thyroid remnant ablation in patients with differentiated thyroid carcinoma

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Introduction
Differentiated thyroid cancers (DTC) are the most frequently occuring endocrine malignancies. The factors determine the recurrences and metastases are whole body scanning (WBS) and either suppressed or stimulated thyroglobulin (sTg) levels. The aim of this study to evaluate the preablative factors predict of radioiodine remnant ablation (RRA) therapy success.
Patients and methods
One hundred consecutive patients with DTC (94 papillary and six follicular) who had undergone total or near total thyroidectomy with no evidence of cervical lymph node and distant metastases were retrospectively evaluated. Stimulated serum TSH and sTg levels were measured before RRA therapy and 6–12 months later. All patients underwent RRA under hypothyroid conditions (TSH >30 μIU/ml). ^{131}I was used 100 mCi as mean dose.
Results
Among patients with DTC the mean age was 49 ± 11.2 years. 87 were females and 13 were males. Eleven patients not included the study because their anti-Tg levels were positive. Preablative Tg levels were higher in patients which 6th month control WBS was positive, but not statistically significant (5.0 (0.6–135.0) vs 1.3 (0.01–99.0), $P=0.06$). Among preablative antiTg positive patients, 6th month WBS involvement rate was significantly higher than negative individuals (44.4 vs 11.3%, $P=0.024$). If postablation WBS revealed multifocal uptake, the 6th month WBS is more likely to be positive (11/51 (21.6%) vs 2/38 (5.3%), $P=0.037$). There were no significant difference on age, tumor size, tumor type, multifocality, anti-Tg, preablative TSH, postablative TSH and sTg between WBS positive and negative patients.
Conclusion
Patients with DTC which had positive antiTg and multifocal involvement in postablative WBS, 6–12 months after ^{131}I remnant radio iodine ablation therapy, revealed that involvement continues. In these patients antiTg levels may affect treatment success. Further studies are needed to evaluate factors determined RRA succes.

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P1131

The role of the transcription factor: Prospero homeobox 1: in the biology of differentiated thyroid cancer

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One of the pathways of DTC dissemination is the lymphatic system, however the molecular basis of this process is still unknown. One of the key regulators of lymphangiogesis is Prospero homeobox 1 (Prox1) specifically expressed in LEC and in some human cancers. The present study investigates the expression and function Prox1 in biology of differentiated cancer cells.
Studies were performed in a series of thyroid cancer FTC and PTC cell lines. Protein and transcript expression levels and intracellular Prox1 localization were determined using molecular biology methods: Q-RT-PCR, western blot and immunocytochemistry. Overexpression of *Prox1* gene was used to determine the role of Prox1 in regulating the hallmarks of malignant cell phenotype (migration, invasion, anchorage independent growth, proliferation and adhesion). We found that Prox1 mRNA and protein were significantly up-regulated in FTC and strongly down-regulated in papillary carcinoma derived cancer cell lines (25-fold). ICC results paralleled Q-RT-PCR and western blot data. Prox1 protein localized in the nucleus or in both cytoplasm and nucleus, depending of cell lines. *Prox1* gene overexpression in TPC1 cells negative for Prox1 increased cellular invasion (fourfold), and colony formation in soft agar. The proliferation and adhesion were moderately- or unaffected.
Prox1, a nuclear transcription factor and a 'master control gene' of lymphangiogenesis is highly expressed in FTC cell lines whereas in PTC derived cells its level is on the limit of the methods used. Transfection of Prox1 to cells deprived its expression, enhanced malignant cells phenotype by induction of invasiveness and colony formation. This may imply essential role of Prox1 in the regulation of malignant cell phenotype. These findings taken together suggest that Prox1 may be involved in differentiated thyroid cancer progression. Further on-going studies will precisely determine the role of Prox1 lymphangiogenesis factor in DTC biology.

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P1132

Treatment outcomes and prognosis of medullary thyroid carcinoma in a tertiary endocrinology center

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A rare and aggressive form of thyroid malignancy, medullary thyroid carcinoma (MTC) is virtually incurable except by complete surgical resection. Due to its insidious onset and extensive spread at diagnosis, its prognosis is often poor.
Aim
To evaluate treatment outcome and prognosis in patients diagnosed with MTC admitted to our department between 2004 and 2013.
Patients and methods
We identified 21 patients (eight men and 13 women) with enough clinical and laboratory data to allow analysis. The average age at diagnosis was 39.9 ± 16.8 years; five patients belonged to MEN2A kindreds with documented RET codon 634 mutation, two to familial MTC kindreds (codon 804 mutation), and 14 patients had sporadic MTC. Evaluation was performed at 3–6 month-intervals in the first 2–3 years after surgery, and included clinical examination, imaging and serial calcitonin (CT).
Results
The onset of symptoms was 15.4 ± 19.9 months before diagnosis, and treatment was further delayed in two asymptomatic MEN2A patients who initially refused surgery. CT at diagnosis was <400 pg/ml in 37.5 and 31.32% were >1000 pg/ml, showing advanced disease. Total thyroidectomy with neck dissection was performed in 67% of patients; 33% required multiple surgeries and only 35% of patients had no local residual/recurrent tumor. CT levels 3–6 months postop were <15 pg/ml in 33.33% and >400 pg/ml in 16.67% – suggesting metastatic spread. In five patients CT decreased after the immediate post-surgery moment (49.3 ± 43.3 vs 36.9 ± 40.3 pg/ml, $P = NS$), suggesting that the 3–6 month interval is more appropriate for testing. Two cases exhibited metastatic disease despite normal CT with rapid progression towards death, suggesting dedifferentiation. At the end of follow-up (82 ± 123.9 months) only 25% of patients had CT <10 pg/ml suggesting cure.
Conclusion
Despite up-to-date diagnostic algorithms and proficient surgery performed in tertiary endocrine centers, the prognostic of MTC is still poor, mostly due to a delayed diagnosis. We advocate for CT measurements in any suspicious thyroid nodule.

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P1133

The presence of $BRAF^{V600E}$ mutation in patients diagnosed of papillary thyroid carcinoma in holycross cancer centre in Kielce, Poland

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Background
The activating somatic point mutation, $BRAF^{V600E}$, is the most common genetic alteration observed in papillary thyroid carcinoma (PTC) but its oncogenic role in PTC has been extensively investigated. Numerous studies reported that $BRAF^{V600E}$ correlates with poor clinical outcome, whereas others have found no such association. It is estimated that $BRAF^{V600E}$ occurs in $\sim$ 45–50% of PTC cases, but recent studies showed the more frequent presence ranging up 87% in some populations.
Objectives
To evaluate the frequency of the mutation $BRAF^{V600E}$ in patients diagnosed of PTC in HCC divided into two groups – low-risk cases defined as micro-PTC pT1a with one carcinoma focus <1 cm without nodal/distant metastases or extrathyroidal extension and the high-risk ones defined as pT_3 at the moment of diagnosis.
Materials and methods
A 405 tissue samples were available of all 675 PTCs diagnosed as pT1aN0-x or pT_3. 62 of the specimens were excluded due to insufficient sample of size to extract DNA or degradation of extracted DNA, leaving 343 tumour samples for *BRAF* analysis. Genotyping was performed on DNA extracted from the thyroid tumour tissue using direct capillary sequencing, and allele-specific amplification PCR was used to resolve equivocal results.
Results
The $BRAF^{V600E}$ mutation was detected in 126 of the 182 diagnosed as pT1aNo-x patients (69.2%) compared to 126 of the 161 diagnosed as pT_3 (78.3%) with no significant difference ($P = 0.0747$).
Conclusions
The presence of $BRAF^{V600E}$ in similar percentage of known low- and high-risk PTC cases may require verifying its usefulness as independent predictor of more aggressive and invasive papillary thyroid carcinoma.

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P1134

Papillary thyroid microcarcinoma: focus on prevalence, characterization and follow-up during a 10 years time period

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Introduction
Recent studies point to an ever increasing papillary thyroid microcarcinoma (PTMC) prevalence, with a percentage range between 20 and 43% of all differentiated thyroid carcinomas. It is many times considered an 'incidental' finding and its clinical behaviour is uncertain.
Aims
To characterize a cohort of patients with PTMC, with reference to clinical and pathological variables and outcome.
Methods
Data from patients with histopathologic diagnosis of PTMC during a 10 years time frame (between Jan-2003 and Oct-2013) were retrospectively reviewed. PTMC prevalence, clinical and histological features were retrieved and final outcome assessed at maximum 10 years follow-up.
Results
Two hundred and sixteen patients, mainly female (85.2%), with a median age of 57-year-old (19–84, min–max), were identified with PTMC. Its prevalence, in respect to the total of thyroid cancers diagnosed in the last 10 years, was 40.1% ($n = 538$). Only 17% had cytological diagnosis of papillary carcinoma preoperatively. Eighty percent of the PTMC were found in surgical specimens of total thyroidectomy and PTMC median size was 5mm, being the classical variant the most common one (79%). It was confirmed tumor extraglandular extension and multicentricity in, respectively, 10 and 29% of cases, with histologically confirmed local lymph node involvement in eight cases (3.7%) and distant metastasis in one case. The median follow-up time of all the sample was 3.5 years. Two patients (1%) presented relapse with histologically confirmed cervical lymph node metastasis, both with <4 years of follow-up. There were no deaths attributed to thyroid cancer during this period.
Conclusion
In this 10-year study, most of the diagnosed PTMC were incidentally found in benign thyroid disease. The relatively uneventful course of PTMC during this time may justify a less intense follow-up.

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P1135

The role of podoplanin in the biology of differentiated thyroid cancers

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Podoplanin (PDPN), a mucine type transmembrane glycoprotein specific to lymphatic system is expressed in a variety of human tumors and regarded as a factor promoting tumor progression. In a recent work, we found PDPN expression in tumor cells of 40% of papillary thyroid carcinomas (PTC), however it role

remains unclear. The purpose of this study was to elucidate the molecular role of PDPN in the biology of thyroid cancer cells.
PDPN gene and protein expression was analyzed in primary thyroid carcinomas and thyroid carcinoma cell lines (TPC1, BcPAP, FTC133, and CGTH-W-1) and NTHY-ori-3-1 cell line by quantitative RT-PCR, western blot, ICC and IHC. To examine podoplanin role in regulating the hallmark of malignant cell phenotype: proliferation, migration, invasion and adhesion of TPC1 cells siRNA silencing of PDPN were analyzed.
We observed that PDPN was solely expressed in cancer cells of 40% of thyroid tumor tissues. Moreover, PDPN mRNA and protein was highly expressed in PTC derived TPC1 and BCPAP, and significantly down-regulated in FTC derived cell lines. Knockdown of *PDPN* with sRNA significantly decreased cellular invasion, modestly reduced cell migration and motility, whereas proliferation and adhesion were not affected.
This is the first study to characterize the expression and function of PDPN in thyroid cancer. Our results demonstrate that PDPN mediates invasion in papillary thyroid carcinomas derived cell lines, suggesting that podoplanin might mediate thyroid papillary carcinoma progression.

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P1136

Prevalence and risk of malignancy of thyroid incidentalomas discovered by ^{18}F-fluorodeoxyglucose positron emission tomography

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The use of ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG–PET) has increased the detection of thyroid incidentalomas (TI). These are associated with a risk of malignancy between 25 and 50%. Some studies show an association between SUVmax uptake and malignancy.
The objective of this study was to determine the prevalence of malignancy on ^{18}F-FDG–PET positive thyroid nodules and to evaluate the relationship between SUVmax uptake and malignancy in a population of patients followed in a central hospital.
We evaluated retrospectively all ^{18}F-FDG–PET exams performed between 2008 and 2013. The inclusion criterion was focal thyroid uptake in patients studied for non-thyroid purposes.
From the 1810 ^{18}F-FDG–PET exams (1384 patients), 3.2% (43) fulfilled the inclusion criteria, 60.5% were females (28), mean age was 68 years. Thyroid ultrasound was done in 39.5% (17) with an average nodule size of 20.5 mm. FNAC was performed in 37.2% (16) with 50% (8) benign, 31% (5) non-diagnostic, 6.5% (1) suspicious for papillary carcinoma and 12.5% (2) papillary carcinoma.
Surgery was performed in the latter two categories, with a histological classification of papillary carcinoma in all three procedures (one with distant metastasis). The median SUVmax was five for the benign cases and 7.95 for the malignant ones ($P=0.38$).
Focal ^{18}F-FDG–PET thyroid uptake had a prevalence of 3.2%. The prevalence of malignancy was 19% on ^{18}F-FDG–PET positive exams. Only 37.2% were evaluated by FNAC. Two possible explanations are the end of life status of these patients but also the lack of knowledge, on non-endocrine services, regarding the risk of malignancy of TI patients. A trend towards a higher risk of malignancy with higher SUVmax was found although it was not statistically significant. The limitations of the current work reflect an undervaluation of patients at risk and the rather high number of non-diagnostic FNAC.

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P1137

Gardner syndrome; a case of presenting with agressive varyant papillary thyroide cancer

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Introduction
Gardner syndrome (GS) have very different extraintestinal manifestations such as include osteomas and thyroid cancers. Thyroid carcinomas associated with familial adenomatozis polyposis coli (FAP), are typically bilateral and multifocal. Our case presenting that GS included Graves' disease (GD) and aggressive varyant of PTC.
Case report
A 43-year-old men admitted to our out patient clinic for thyrotoxicosis investigation. He was complaining of related to thyrotoxicosis such as tremor and anxiety. On physical examination, her thyroid gland was grade two diffuse palpable and bilateral Graves' ophtalmopathy. There were osteoma of fifth metatarse and surgery of proflactic colectomy for FAP in his background. His thyroid hormone values were sT_3: 13.85 pg/ml (2–4.4), sT_4: 3.45 ng/dl (0.93–1.7), and TSH <0.005 μIU (0.27–4.2). The thyroid and servical USG showed diffuse thyroid gland enlargement and diffuse microcalcifications lesions in parenchymal and metastasis of bilateral cervical lymph node. Finally, it was diagnosed with GS which included FAP and osteoma. USG guided fine needle aspiration biopsy of the microcalsification of parenchymal and bilateral cervical lymph node was performed. The cytopathologic evaluation revealed suspicion of malignancy for the biopsy of parenchymal and metastasis of central and bilateral cervical lymph node. Total thyroidectomy and bilateral central lymph and cervical lymph node dissection was performed by surgeon. The largest diameter of the thyroidectomy specimen was $5.5\times3.5\times3$ cm in the right lobe, $4.5\times3.5\times3$ cm in the left and $4.5\times2\times2$ cm in isthmus. Microscopic examination showed classical and tall cell variant of PTC. The presence of mix variant of PTC was diffuse, capsular invasion and lymphovascular permeation(Fig 1).
Result
Prognosis for PTC in GS is similar to sporadic PTC. Papillary thyroide cancer may become more aggressive in GD. Because of this we think that the cause of aggressive clinical behavior of PTC in our case may be related to whose GD.

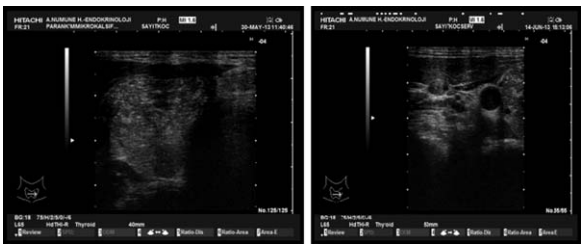

Figure 1

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P1138

Prognostic factors in 213 patients with differentiated thyroid cancer

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Objectives
Prognosis of differentiated thyroid carcinoma (DTC) is usually good, but even so a proportion of the patients develop recurrences and eventually die of the disease. The aim of this study was to analyze the clinical and histopathological features of patients with DTC in our center and to identify prognostic factors in this group of patients.
Patients and methods
We reviewed, retrospectively, 213 patients (184 females and 29 males, mean age 48.8 years, range 19–86) with DTC (192 papillary and 21 follicular carcinoma) who were treated in our hospital from 1992 up to 2012. Total thyroidectomy was performed in 186 patients (87.3%), bilateral near total thyroidectomy in nine of them (4.2%) and hemithyroidectomy in 18 patients (8.4%). Lymphadenectomy was carried out in 80 patients (37.5%). The mean follow-up period was 6.83 years (1–20 years) and the patients were ranked by the pTNM system. Survival probability was calculated using Kaplan–Meier analyses. Prognostic factors were analyzed using a univariate log rank test and a multivariate Cox regression analysis model.
Results
Fifteen patients (7.04%) had local or distant recurrences, which nine of them had locoregional metastases, the mean time to recurrence being 61.3 months. The 10 years overall survival rate for the entire group was 89%, with a mean survival time of 17.5 years. The factors affecting 10 years disease-free survival were T_4a, soft tissue invasion, lymph node metastasis and involvement of more than five nodes. The factors that better predicted the DTC recurrence in a multivariate

analyses were nodal involvement (HR 4.86, CI 1.42–16.54, *P* 0.01) and soft tissue invasion (HR 4.49, CI 1.21–16.65, *P* 0.02). The only factor that affected overall survival was vascular invasion.

Conclusions

In our series, lymph node metastases and soft-tissue involvement were associated with an increased risk of recurrence while vascular invasion was the factor related to a higher risk of death.

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P1139

The effect of allelic variants of the thyroid hormone receptor β (*THRB*) gene on the incidence of papillary thyroid carcinoma

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Objectives

Papillary thyroid carcinoma (PTC) is the most common malignancy of the endocrine system. Its heritability is the highest among common cancers, as evidenced by family-based studies. Thyroid hormone receptor β gene (*THRB*), a known tumor suppressor, is crucial for the proper thyroid function, therefore its polymorphisms are likely to affect the risk for thyroid cancer.

Aim of the study

In order to identify alleles that might modify the risk and clinical presentation of PTC we genotyped the three functional SNPs of *THRB*, namely rs13066296, rs13097208 and rs6792725.

Materials and results

DNA extracted from blood of 1683 PTC patients and 1667 control subjects was analyzed by Sequenom iPLEX technology. The association study revealed a significant association between the rs6792725 GG genotype of the *THRB* gene and a risk of development of PTC (OR = 1.20; 95% CI: 1.05–1.39; $P = 0.0078$). The study also showed a significant association between the CTG haplotype (rs13066296–rs13097208–rs6792725) and a higher risk of development of PTC (OR = 1.15; $P = 0.047$). Clinical phenotype was found to be influenced by interactive impact of the SNPs in combination with gender. rs13066296 variant modifies the likelihood of more advanced disease in males compared to women. The risk for worse *T*-status significantly decreases with each additional variant allele (hetero- or homozygous state) in males compared to females ($P = 0.023$). Moreover, analysis of interaction between rs13097208 and age revealed an interactive, protective impact on clinical stage. The risk of worse clinical stage significantly decreases in the presence of rs13097208 variant allele ($P = 0.034$).

Conclusions

This is the first study identifying a polymorphism and a haplotype within the *THRB* gene that significantly predisposes to the development of PTC in a Polish population, and an important step in understanding the background of genetic predisposition to PTC.

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P1140

Thyroglobulin before radio remnant ablation during levothyroxine withdrawal can be considered an accurate parameter of remission of differentiated thyroid cancer

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Introduction

Differentiated thyroid cancer (DTC) is the most frequent endocrine cancer. After surgery followed, if any, by ^{131}I radio remnant ablation (RRA), follow-up monitoring consists of neck ultrasonography (US) and measurements of thyroglobulin (Tg) levels and anti-Tg antibodies (Ac-Tg) both on levothyroxine (L-T_4) therapy and after recombinant TSH (rTSH). The aim of our study is to define a cut-off of Tg before RRA (RRA-Tg) during L-T_4 withdrawal predictive of remission of disease.

Materials and methods

We prospective evaluated 113 patients who underwent total thyroidectomy with or without lymphadenectomy for DTC. All patients received RRA after surgery, without evidence of iodine uptake outside neck. Ac-Tg were negative. Tg after rTSH stimulation (rTSH-Tg) was performed 9–12 months after RRA. During follow-up patient was considered 'free of disease' on the basis of undetectable Tg values on suppressive L-T_4 therapy (L-T_4-Tg), rTSH-Tg < 2 ng/ml, negative Ac-Tg and negative neck US.

Results

RRA-Tg was between 0.5 and 117 ng/ml (mean ± S.D.: 7.52 ± 14.06); L-T_4-Tg was between 0.01 and 1.00 ng/ml (mean ± S.D. 0.15 ± 0.20); rTSH-Tg was between 0.02 and 15.00 ng/ml (mean ± S.D.: 0.58 ± 2.06). 107 patients (94.7%) showed rTSH-Tg ≤ 2 ng/ml; six patients (5.3%) had rTSH-Tg ≥ 2 ng/ml. ROC curve demonstrated that RRA-Tg can be considered highly predictive of negative rTSH-Tg. In particular, for RRA-Tg values of 10 ng/ml sensitivity and specificity are of 100 and 83% respectively; for RRA-Tg values of 18.35 ng/ml sensitivity and specificity are of 100 and 95% respectively.

Conclusions

RRA-Tg can be considered an accurate parameter to predict the remission of DTC. For RRA-Tg values < 18.35 ng/ml, during subsequent follow-up the possibility to avoid rTSH-Tg test should be considered in presence of undetectable L-T_4-Tg levels, negative Ac-Tg and negative neck US.

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P1141

The usefulness of thyroid function tests for the estimation of individual sensitivity to levothyroxine therapy in patients with thyroid cancer

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Introduction

The long-term follow-up of the patients with well-differentiated thyroid cancer (WDTC) includes the monitoring of suppressive levothyroxine therapy. Our study evaluated the peculiarities of thyroid status in WDTC patients on the doses of levothyroxine leading to TSH suppression (lower than 0.5 mI/l).

Study design

We have studied 114 patients with WDTC, 24 men and 90 women. The follow-up was a least 10 years after thyroid surgery, mean age at the study was 28.42 ± 0.29 years. The mean daily levothyroxine dose was 2.65 ± 0.05 μg/kg. The control group presented with age and sex-matched healthy subjects. The estimation of thyroid function tests was done using ELISA-kits (DRG, USA).

Results

In WDTC patients, 24 h after the last levotyroxine dose, the mean TT_4 and FT_4 levels were 30 and 20% higher compared to the control; FT_3 levels did not differ. The most frequent hormonal changes were as follows: TT_4 elevations – 46.5%, FT_4 – 18.4%, and FT_3 – 10.5%. An elevated T_4 was more frequent in female patients compared to male ones (51.5 vs 29.2%). On the contrary, FT_3 elevation was detected more often in man than in woman (20.8 vs 7.8% respectively). In the subset of patients with an increased FT_3, the statistically lower total cholesterol level was revealed compared to the patients with normal levels of the thyroid hormones; however, the mean levothyroxine doses did not differ significantly in two subgroups.

Conclusion

A proportion of WDTC patients–who receive 2.65 ± 0.05 μg/kg of levothyroxine and have TSH suppression lower than 0.5 mI/l–simultaneously have an elevated FT_3 levels. Such patients may have a higher individual sensitivity to thyroid hormone's action and need an individual dose correction during their monitoring to provide an optimal hormonal and metabolic control.

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P1142

Polymorphic pre-miR-146a and synergistic action of all of its products on NTRK2 gene in papillary thyroid carcinoma

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Objectives
Aberrances in expression and sequence of miR-146a have a well-established role in pathogenesis of papillary thyroid carcinoma (PTC). The G/C heterozygosity in rs2910164 of miR-146a underlies genetic predisposition to PTC and occurs as a somatic mutation in thyroid tumors. Deleterious function of rs2910164 consists in creation of a new variant of microRNA, resulting from the fact that a single microRNA precursor gives rise to −5p and −3p microRNAs. The SNP is located in the seed region (responsible for target gene recognition) of miR-146a-3p, thus its presence generates two isoforms that regulate distinct sets of target genes. As a result, heterozygous carriers of the SNP produce three mature miRs: miR-146a-5p, miR-146a-3p (G) and 146a-3p (C). Interestingly, there is only one gene concertedly targeted by the three isoforms, and its deregulation can underlie the miR-146a-dependent predisposition to PTC.
Aim
The aim of this project was to analyze the synergistic action of isoforms of polymorphic miR-146a on the expression of their shared target gene – NTRK2 - and to determine the role of this process in thyroid carcinogenesis.
Methods and results
In silico analysis revealed that all three isoforms of miR-146a potentially target one gene – NTRK2, coding for a member of the high-affinity neurotrophin receptors with tyrosine kinase activity, that controls differentiation and programmed cell death. Binding of miR-146a to 3′ UTR of NTRK2, analyzed in luciferase assay, resulted in a 30% ($P=0.0037$) reduction of luciferase activity. NTRK2 expression quantified in 58 pairs of PTC and unaffected tissue samples revealed that NTRK2 levels were significantly, twofold decreased in 93% of tumors ($P=4.75\times10^{-7}$).
Outcome
This is the first functional study of the synergistic effect exerted by polymorphic miRNAs produced from a single precursor. Results of the analysis may give a strong basis for better understanding of the role of miR-146a and NTRK gene in development of PTC.

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P1143

Post-ablative thyroglobulin level as a predictor of favourable prognosis in patients with differentiated thyroid cancer

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Introduction
Postoperative thyroglobulin (TgPO) has a well established position as the prognostic factor for the follow-up of patients with differentiated thyroid cancer (DTC) after total thyroidectomy. However, the presence of thyroid remnants after surgery may diminish predictive value of TgPO.
The aim of the study is to evaluate prognostic value of stimulated postablative thyroglobulin level (TgPA) measured after 6–9 months after radioacitve iodine ablation, and its possible superiority to TgPO assessment.
Material
The study involved 1200 patients with DTC, treated in the Holycross Cancer Centre in Kielce in the years 2000–2013. Exclusion criteria were: patients with no recommendation for radioactive iodine therapy; positive thyroglobulin antibodies; initial distant metastases and patients who did not attend their appointments.
Methods
Both TgPO and stimulated TgPA levels were retrospectively studied. Considering further clinical follow-up and using ROC curve analysis, the TgPO and TgPA levels, which reliably predict favourable diagnosis, were assessed and compared.
Results
TgPO level $\leq$6.99 ng/ml with sensitivity of 75.7% and specificity of 94.7% enables to predict remission of the disease.
TgPA level $\leq$1.16 ng/ml under TSH stimulation induced by thyroid hormone withdrawal enables to predict remission of the disease with sensitivity of 91.1% and specificity of 94.7%.
TgPA level $\leq$1.24 ng/ml under rhTSH stimulation enables to predict remission of the disease with sensitivity of 95.4% and specificity of 95.0%.
Conclusions
No significant difference in clinical usefulness of determining TgPO and stimulated TgPA levels was revealed in terms of remission of the disease. However stimulated TgPA level $\leq$1.24 ng/ml with higher sensitivity predicts favourable prognosis.

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P1144

Coexistence of mutations in the CHEK2 and BRAF^{V600E} genes and their impact on the course of the papillary thyroid carcinoma (PTC)

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Introduction
The activating BRAF^{V600E} is the most common genetic alteration in PTC. There is a common belief that it can correlate with a more aggressive clinical course. The mutation of the CHEK2 gene impairs the repair processes of the damaged DNA. It can be expected that the coexistence of both mutations can be related to a worse clinical course.
Aim
To assess the prevalence of the coexistence of the CHEK2 and BRAF^{V600E} mutations and their impact on the severity of the PTC.
Material
The study consisted of 201 patients with PTC, females: 180 (89.6%), males: 21 (10.4%), aged 15–74 years.
Methods
Patients underwent testing of the CHEK2 gene using PCR-HRM and sequencing of DNA isolated from peripheral blood. The presence of the BRAF^{V600E} mutation was evaluated by direct sequencing. Patient's age and disease severity at diagnosis and the coexistence of the CHEK2 and BRAF^{V600E} mutations in the evaluated group was assessed.
Results
Coexistence of the CHEK2 and BRAF^{V600E} mutations was found in 28/201 patients (13.9%). The CHECK2 alone was found in 13/201 (6.5%) and the BRAF^{V600E} mutation alone was found in 109/201 (54.2%), 51/201 (25.4%) patients had no mutation. There was no significant difference in age, sex in particular groups. Stage of the disease progression in the group with coexistent CHEK2 and BRAF^{V600E} mutations: I-71.4%; II-3.6%; III-17.9%; IV-7.1%; in 109 patients with the BRAF^{V600E} mutation alone: I-62.4%; II-1.8%; III-34.9%; IV-0.9%; in 13 patients with the CHEK2 mutation alone: I-69.2%; II-15.4%; III-7.7%; IV-7.7%; in 51 patients without mutation: I-82.3%; II-0%; III-11.8%; IV-5.9%. The reported difference was not statistically significant.
Conclusions
i) Coexistence of the CHEK2 and BRAF^{V600E} mutations was found in 13.9% PTC patients.
ii) There was no observed influence of the coexistent CHEK2 and BRAF^{V600E} mutations on the severity of the disease at diagnosis.
iii) Further research on larger group are necessary to evaluate the significance of the coexistence of both analyzed mutations.

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P1145

Impact of different methods on the detection frequency of *BRAF* mutation in papillary thyroid carcinoma

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Introduction
Still there is a discussion about the importance of diagnostic and prognostic relevance $BRAF^{V600E}$ mutation. The wide range of $BRAF^{V600E}$ mutation frequency (40–80%) doesn't facilitate this task. Population diversity and genotyping methodology are suspected sources of differences seen in the mutation frequencies detected by different studies. The aim of this study was to assess the prevalence $BRAF^{V600E}$ mutation depending on the diagnostic method used.
Methods/design
Tumors from 411 consecutive patients with PTC genotyped for $BRAF^{V600E}$ using capillary sequencing and ASA-PCR.
Results
Of the 411 cases genotyped using both methods capillary sequencing and ASA–PCR $BRAF^{V600E}$ mutation detected in 270 cases (65.7%) and 8 (1.9%) other mutations detected in the *BRAF* near codon V600 (total 278 (67.6%) mutations). In contrast, no mutations were found in 121 (29.4%) cases. DNA degradated in 12 (2.9%) cases. If we take into account only the results obtained by sequencing $BRAF^{V600E}$ mutation detected in 186 (45.3%) cases and 8 (1.9%) other mutations in the vicinity of codon $BRAF^{V600E}$. In total sequencing detected 194 (47.2%) mutations in the *BRAF*. In 151 (36.7%) cases no mutation detected. In 31 (7.5%) cases sequencing result was inconclusive. DNA degradated in 35 (8.5%) cases. However, with the ASA-PCR method $BRAF^{V600E}$ mutations were found in 270 (65.7%) cases. This method only detects the V600E mutation, so it hasn't detected eight cases with mutations located in the vicinity of the *BRAF* V600. In 27 (6.6%) cases the DNA was degraded and one result was inconclusive.
Conclusion
The frequency of detected mutations in the *BRAF* depends on the method. The combination of methods with different sensitivity and spectrum of detected mutations increases the incidence of PTC with $BRAF^{V600E}$. Differences in the frequency of BRAF mutations in PTC described the literature may be the result of applied research methodology.

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P1146

Long-term follow-up of young patients submitted to radiotherapy: analysis of ten thyroid cancer cases

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Introduction
The increasing risk of thyroid cancer (TC) in patients who underwent radiotherapy is well documented, especially at early ages. In our center, young patients undergoing cancer treatments are referenced to Endocrine Rehabilitation Clinics (ERC). Their risks are initially identified and monitored regularly. We intended to analyze the characteristics and outcomes of patients who developed post-radiotherapy TC.
Methods
Medical records of patients registered in ERC who underwent radiotherapy and developed TC were reviewed.
Results
Ten patients (seven females) were identified. Primary diagnoses: five Hodgkin's lymphoma, one abdominal lymphosarcoma, three acute lymphoblastic leukemia and one medulloblastoma, mean age at primary diagnosis 9 ± 5.6 years. Radiotherapy sites: one cervical, four cervico-mediastinic, one abdominal, one total body irradiation, two CNS, one CNS + neuro-axis; mean RT dose: 24 ± 8.4 Gy; mean age at last treatment: 10 ± 5.5 years. None showed thyroid dysfunction. Average time until the first thyroid nodule: 14 ± 4.7 years; seven patients with a dominant nodule and three with ≥ 2 nodules; mean nodule's size increment: 2.4 ± 1.6 mm/year. First cytology results: six colloid nodules, two papillary thyroid carcinoma (PTC), one follicular neoplasm and one unknown. Colloid nodule ctyologies were reviewed by a pathologist who found no differences from patients without radiotherapy history. Seven patients underwent total thyroidectomy and three thyroidectomy + lymphadenectomy; mean age at surgery: 27.9 ± 9.2 years. All patients with histology of PTC: eight in stage I and two in II. Iodine-ablation therapy was performed in all patients. Currently, they're all in remission. Median follow-up from primary to histological diagnosis of PTC: 20 years; median PTC follow-up: 3 years.
Conclusion
TC is a late radiotherapy complication, even when the gland is not directly irradiated. These cancer survivors must be regularly monitored once these nodules are at high risk of malignancy.

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P1147

Occurrence other than V600E mutation in the *BRAF* gene in papillary thyroid carcinoma

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Introduction
$BRAF^{V600E}$ mutation constitutes 98–99% of all detected mutation in thyroid carcinoma. The remaining 2% are *BRAF* mutations detected in the vicinity of codon V600. Due to the low incidence not much is known about their importance for the development of papillary thyroid carcinoma (PTC). In addition, some of these mutations co-occur with the mutation $BRAF^{V600E}$.
Methods/design
The study presents 15 cases with mutations other than $BRAF^{V600E}$ detected during routine diagnostics of 485 cases of PTC using direct sequencing. For comparative analyzes we used published literature data.
Results
Among the 15 mutations analyzed, three mutations ($2\times$p.V600_K601delinsE and p.T599_V600insT) already detected in the PTC. In contrast, mutations: p.G593S, p.F610S, p.L588P, p.L584F, p.F595L, p.D594N and p.S616F already have been described in cases of malignant melanoma. Other mutations: p.V600_604WdelinsE, p.598_599insI, p.E611K, p.S614F, p.H608Y, p.G615E weren't detected previously in PTC. However, in those codons previously described different amino acids changes in malignant melanoma and PTC. In six cases of PTC in addition to V600E other mutations detected: p.E611K, p.L588P, p.V600_K600EdelinsE, p.H608Y, p.S616F and in one case even two additional: p.G593S, p.F610S.
Conclusions
Mutations other than $BRAF^{V600E}$ are relatively rare (2–3% of *BRAF* mutation in PTC) and predominantly locate in the vicinity of the codon V600. Literature review suggests that some have already been described in the PTC and in other tumors (malignant melanoma, pancreas and large intestine). This suggests that these mutation could have oncogenic potential which may be responsible for oncogenesis of PCT. The presence of more than one mutation suggests the clonality and active process of tumorigenesis in PTC, which could be important for clinical outcomes. However, for a comprehensive explanation of the significance of these mutations in the oncogenesis of PTC we need more basic research.

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Does lymphocytic thyroiditis influence the histological characteristics and the course of thyroid carcinoma in children and adolescents?

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Introduction
The aim of the present study was to evaluate if demographic and histological characteristics as well as the long-term outcome of thyroid cancer was different in children and adolescents with and without autoimmune thyroiditis taking into consideration that information in the literature is scarce.
Methods
The medical records of children and adolescents ($\leq$21-year-old) followed up in Theagenio Cancer Hospital due to histologically proven thyroid carcinoma were reviewed. The following data were recorded: year of diagnosis of thyroid cancer, age at diagnosis, gender, family history of thyroid cancer, history of external radiation therapy, histological type (papillary and variants, follicular, medullary and poorly differentiated), tumour size, multifocality, lymph node metastases, vascular invasion, infiltration of thyroid parenchyma or surrounding soft tissues and presence of distant metastases. Information about the presence of anti-Tg and

anti-TPO was also collected. All histological material was reviewed by a second pathologist with special attention in order to identify findings of lymphocytic thyroiditis. Data analysis was performed using the statistical package SPSS.
Results
One hundred and twelve children and adolescents (mean age 18.1 ± 3.0 years) were diagnosed with thyroid cancer from 1980 to 2013. Histology revealed papillary thyroid carcinoma (PTC) in the majority of the cases (88.4%). Thirty two patients (28.6%) presented histological characteristics compatible with lymphocytic thyroiditis. No differences were found in anthropometric characteristics between patients with and without lymphocytic thyroiditis. Infiltration of thyroid parenchyma was more frequent in the Hashimoto thyroiditis group compared to patients without (75.0 vs 47.5% respectively, $P=0.015$). Familial PTC was more frequent in patients with lymphocytic thyroiditis compared to those without lymphocytic thyroiditis (22.2 vs 2.8% respectively, $P=0.006$).
Conclusion
Children and adolescents with Hashimoto disease present more frequently familial PTC as well as thyroid cancer with invasive characteristics. Larger epidemiological studies are needed to confirm our results.

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Prognostic significance of TERT promoter mutations in follicular cell-derived thyroid carcinomas

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Context
Telomerase promoter mutations (*TERT*) were recently described in follicular cell-derived thyroid carcinomas (FCDTC) and seem to be more prevalent in aggressive cancers.
Objectives
We aimed to evaluate the frequency of *TERT* promoter mutations in thyroid lesions and to investigate the prognostic significance of such mutations in a large *cohort* of patients with differentiated thyroid carcinomas (DTC).
Material and Methods
We studied 647 tumours and tumour-like lesions. A total of 469 patients with FCDTC treated and followed in five University Hospitals were included. Mean follow-up (±s.d.) was 7.8 ± 5.8 years. We evaluate the predictive value of *TERT* promoter mutations and other clinico-pathological and molecular features (*BRAF*, *NRAS*) for distant metastasization, disease persistence at the end of follow-up and disease-specific mortality.
Results
TERT promoter mutations were found in 7.5% of papillary carcinomas (PTC), 17.1% of follicular carcinomas (FTC), 29.0% of poorly differentiated carcinomas and 33.3% of anaplastic thyroid carcinomas. Patients with *TERT*-mutated tumours were older ($P<0.001$) and had larger tumours ($P=0.002$). In DTC, *TERT* promoter mutations were significantly associated with distant metastases ($P<0.001$) and higher stage ($P<0.001$). Patients with DTC harbouring *TERT* promoter mutations were submitted to more radioiodine treatments ($P=0.009$) with higher cumulative dose ($p=0.004$), and to more treatment modalities ($P=0.001$). At the end of follow-up, patients with *TERT*-mutated DTC were more prone to have persistent disease ($P=0.001$). *TERT* promoter mutations were significantly associated with disease-specific mortality [in the whole FCDTC ($P<0.001$)] in DTC ($P<0.001$), in PTC ($P=0.001$) and in FTC ($P<0.001$). After adjusting for age at diagnosis and gender, the HR was 10.35 (95%CI 2.01–53.24; $P=0.005$) in DTC and 23.81 (95%CI 1.36–415.76; $P=0.03$) in PTC.
Conclusions
TERT promoter mutations are an indicator of clinically aggressive tumours, being correlated with worse outcome and disease-specific mortality in DTC. *TERT* promoter mutations have an independent prognostic value in DTC and, notably, in PTC.

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BRAF V600E genetic mutation analysis in patients had been diagnosed of unknown malignancy potential thyroid tumors and papillary thyroid microcarcinoma

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Aim
The purpose of this study was to analysis BRAF V600E mutational status in papillary thyroid microcarcinomas (PTMCs) and unknown malignant potential thyroid tumors (UMP-TTs) and to investigate association of BRAF V600 positivity with clinicopathologic parameters.
Material and method
Seventy-two PTMC and 20 UMPTT tissues were included in this study. Genomic DNA was extracted from paraffin-embedded tumor tissue. The paraffin-embedded thyroid tumor samples were cut into 5 μm sections. The tumor areas dewaxed and dissected. DNA was isolated using QIAamp DNA-FFPE tissue kit. We amplified exon 15 of the *BRAF* gene, which contains the BRAF V600E mutation with RFLP analysis by using the following primers. The PCR products were electrophoresed in polyacrilamide gel. Samples were stained with silver nitrate and imaged.
Results
BRAF V600E mutation frequency in PTMCs was 41.6% (72/30), in unknown malignant potential well differentiated tumors (UMP WDT) was 80% (10/8). The BRAF V600E mutation was significantly associated with the classic variant of PTC 73.3% ($P=0.047$). BRAF positivitiy in PTMCs was significantly related to invasion of thyroid capsule 66.67% ($P=0.003$) and absence of the tumor capsule 80% ($P=0.003$). There was no significant correlation between the occurence of BRAF V600E mutation and advanced disease stages, extrathyroidal extension, cervical lymph node metastasis, age, gender, multifocality in PTMCs. The odd ratio for female sex in BRAF positive PTMCs was 2.46 for Hashimoto thyroiditis in BRAF positive PTMCs was 2.12.
Conclusion
BRAF V600E mutation was significantly associated with the classic variant, absence of the tumor capsule and penetration of the thyroid capcule in PTMCs. UMP-WDT lesions of the thyroid with BRAF mutation may represent PTC precursors or less aggressive type of PTCs. Tumor recurrence and poorer prognosis wasn't associated with BRAF V600E mutation after a median follow-up of 22 months.

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Prognosis of papillary thyroid cancer with lung metastasis at diagnosis

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Introduction
Subjects with papillary thyroid cancer (PTC) usually have a long survival time after diagnosis. However, the prognosis of PTC subjects with lung metastasis noted at the time of initial diagnosis is unknown.
Material and methods
From 1998 to 2009, patients with PTC were recruited by medical chart review. Patients with lung metastasis at initial diagnosis (PTC-L) were identified. Their follow-up courses were evaluated and compared to patients without lung metastasis (PTC-NL).
Results
There were 453 patients with PTC. Among them, 15 (3.3%) had lung metastasis at initial diagnosis. Compared with PTC-NL, PTC-L patients were older (mean age 61.3 ± 13.8 years, $P=0.0005$). There were no difference among gender (male 4.8 vs 2.7%, $P=0.3764$), tumor size (2.1 ± 1.7 vs 2.5 ± 1.6 cm, $P=0.3578$) or

lymphnode involvement (60 vs 56.9%, $P=0.8085$) between PTC-L and PTC-NL. The mean follow-up period was 3.2 ± 2 years (range 0.3–6.7 years) for PTC-L patients and 3.4 ± 2.6 years (range 0.04–12.1 years) for PTC-NL patients. During the total follow-up period of 1558 person years, 1 PTC-L patient and 5 PTC-NL patients died. The difference was borderline significant (log-rank test, $P=0.0506$).
Conclusion
PTC-L patients were older than PTC-NL patients. The survival time of PTC-L and PTC-NL patients was borderline significantly different.

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Gene expression signature associated with BRAFV600E mutation in human papillary thyroid carcinoma based on transgenic mouse model

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Objectives
Recent studies on BRAFV600E mutation, known as initiating event in papillary thyroid carcinoma (PTC) and related to more aggressive clinical course of the disease, revealed its significant influence on gene expression profile suggesting that BRAF(+)PTCs represent a molecular subtype of PTC. However, the human material disables distinction of possible molecular causes of cancer from its effects, unlike the mouse model. The main goal of our project was to find genes deregulated in a BRAFV600E-dependent manner in human PTCs using the transgenic mouse model of BRAF-induced PTC.
Material and methods
The mice material included ten BRAF(+)PTCs, ten BRAF(+)borderline lesions, four BRAF(+) and four BRAF(−) colloid goiters (CG), five BRAF(+) and five BRAF(−) healthy thyroids (HT). The human material consisted on Polish cohort of patients (31 PTCs, 18 healthy thyroids) and data made available by Giordano *et al*. (41 PTCs). The microarray data were obtained with the Affymetrix platform. The bioinformatical analysis was oriented on finding BRAF-specific genes from CG and HT mice samples and verifying them on the human dataset. The potential differences between gene signatures of human PTCs with distinct molecular events have been analyzed as well. The microarray data were validated with the QPCR.
Results and conclusions
Over 800 genes were deregulated between BRAF(+) and BRAF(−) CG and HT mice samples. The analysis of distinct molecular PTC subtypes in human samples revealed that expression profile of obtained signatures for BRAF(+)PTCs and PTCs with RET rearrangements are more similar to each other than to RAS(+) PTCs. The last ones are much closer in their gene expression profile to WT-PTCs and healthy thyroids. Finally, 18 genes were selected as deregulated in BRAF(+) PTCs in comparison to each of the analyzed group. Next, 57 genes, differentially expressed between BRAF(+)PTCs and other groups except of RET(+)PTCs, are described.

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